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HISTOPATHOLOGIC EFFECT OF ANOXIA ON THE CENTRAL NERVOUS SYSTEM

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BOSTON

Damage to the nervous system as a consequence of anoxia has been produced in many ways, but most of the investigations dealing with this subject have borne but slight relation to the problem of aviation Illuminating and important as many of these previous clinical and experimental studies have been, they have not, with few exceptions, been concerned with precisely the conditions met with in aviation The purpose of the present investigation was to determine whether histologic alterations were produced in the central nervous system after repeated, sublethal exposures to an atmosphere deficient in oxygen, to measure the amount of oxygen to which the nervous system was exposed, and to correlate that amount, if possible, with the nature of the histologic process The extensive use of the high flying airplane in war, with its accompanying hazards of failure of oxygen supply, jumps from high altitudes and the possible cumulative effect of the chronic day by day exposure to fatigue and anoxia, makes the need for such an investigation imperative It is well known [1] that acute and chronic altitude sickness was a major problem in the first world war and in commercial aviation after the war, and while greatly improved precautionary measures are in use at the present time, the possibility of neurogenic deterioration among pilots and other fliers has in no sense been eliminated [2] An attempt has been made, therefore, to investigate the effect on the brain of repeated exposures to degrees of anoxia which in a single exposure would have but transient effect

The different conditions under which anoxia of the nervous system has been produced may be grouped under the classification of anoxias as suggested by Barcroft,[3] or by Peters and Van Slyke [4] 1 Anoxic anoxia is characterized by low oxygen tension of the arterial blood, so that the hemoglobin does not have its normal degree of oxygen saturation 2 Anemic anoxia is a condition in which insufficient amounts of hemoglobin are available for oxygen transport even though the oxygen tension is normal 3 Stagnant anoxia is the result of defective circulation of blood during which the tissues fail to receive an adequate supply of oxygen even though the arterial blood contains sufficient oxygen in the proper degree of saturation 4 Histotoxic anoxia occurs when the tissue cells themselves are unable to utilize oxygen even though it is available in the arterial blood

As a frame of reference this classification has a good deal of practical value Since the methods of producing the various kinds of anoxia differ from one another, the local physiologic effects on the brain are not exactly the same, and, consequently, the resulting pathologic lesions show certain variations with the different types of anoxia While it is not always possible to identify the type of anoxia from the nature of the neuropathologic lesion, there are certain characteristic features that are of value Without anticipating the results of this experiment, it may be pointed out, for example, that zones of laminar cortical necrosis were found in a monkey that had been subjected to anoxic anoxia in a decompression chamber and these lesions were apparently identical with those reported by Courville [5] in cases of anoxic anoxia incident to nitrous oxide anesthesia On the other hand,

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1 Armstrong, H G Anoxia in Aviation, J Aviation Med **9** 84, 1938

2 Jokl, E Medical Problems of Aviation, J Roy Army M Corps **73** 289, 1939

3 Barcroft, J Anoxemia, Lancet **2** 485, 1920

4 Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol 1, p 1264

5 Courville, C B Asphyxia Following Nitrous Oxide Anesthesia, Medicine **15** 129, 1936

it should also be pointed out that a case can likewise be built up for the fact that certain overlapping similarities in the pathologic picture of the different types of anoxia do occur, depending, at least in part, on the intensity of the exposure, the cumulative effect and the duration of the survival While it is difficult to compare the lesions of acute stagnant anoxia following vascular occlusion, such as those reported by Gildea and Cobb,[6] with the early lesions of anemic anoxia produced by inhalation of carbon monoxide[7] because of the difference in time during which the anoxia was effective, it is nevertheless true that shrunken and deeply stained nerve cells were the changes first seen with both types of anoxia Other similarities will be discussed later

There is an extensive literature covering the effects of all these types of anoxia on the central nervous system a critical review of which will be entirely omitted from this paper The interested reader can readily orient himself by consulting a few key references to the various types of anoxia For information on stagnant anoxia, ligature type, de Buck and de Moor[8] Gildea and Cobb,[6] Tureen[9] and Weinberger and the Gibbons[10] may be consulted. Anemic anoxia, inhalation type, has been covered by Ruge,[11] Ferraro and Morrison,[7] Sayers and Davenport[12] and many others Histotoxic anoxia has been well studied by Ferraro[13] and by Hurst[14] while information on the effects of anoxic anoxia on the central nervous system has been reviewed and added to by Courville,[5] Armstrong and Heim,[15] Thorner and Lewy[16] and others The observations of these and other investigators will be referred to when necessary, but, for the sake of brevity, their work will not be discussed at this time

MATERIALS AND METHODS

An air-tight chamber made of steel and glass, modeled after the one used by Hastings and associates,[17] was used as a gassing compartment for some of the animals Air was mixed with nitrogen through the medium of an oxygen concentration meter[18] and introduced into the chamber Carbon dioxide was removed from the chamber atmosphere by circulating the chamber gas through a soda lime tower It was attempted to cool the chamber atmosphere by passing the circulating gas through a copper coil immersed in ice water Samples of the gas mixture for analysis were obtained from the chamber atmosphere The hindquarters of the dog were drawn through an air-tight rubber sleeve in one side of the chamber, so that blood could be obtained from the femoral artery

Most of the animals, however, were given the gas mixture by means of a mask This was found satisfactory after a brief preliminary training The dog was secured in a recumbent position to an animal operating table, and an air-tight gas mask was strapped over his mouth and nose The mask was made of heavy celluloid and was made air tight in relation to the dog's head by means of an air-inflated rubber cushion The mask was equipped with one inlet and one outlet unidirectional valve Air was mixed with nitrogen through the same kind of oxygen concentration meter as that used with the chamber Samples of the air-nitrogen mixture were taken for analysis from a collecting bag attached to the gas mask There was no rebreathing, for the outlet valve had no egress to the collecting bag, so carbon dioxide did not accumulate Blood was obtained from the femoral artery The oxygen and carbon dioxide contents of the gas mixture were determined by the method of Haldane[19] and those of the blood by the method of Van Slyke-[20] Hematocrit readings were usually made, and on certain occasions determinations of sugar content were carried out

Twenty-five dogs were exposed to such atmospheres deficient in oxygen The exposures were usually made

6 Gildea, E F, and Cobb, S The Effects of Anemia on the Cerebral Cortex of the Cat, Arch Neurol & Psychiat **23** 876 (May) 1930

7 Ferraro, A and Morrison, L R Illuminating Gas Poisoning An Experimental Study of the Lesions of the Nervous System in Acute and Chronic Stages, Psychiatric Quart **2** 506, 1928

8 de Buck, D, and de Moor, L Lesions des cellules nerveuses sous l'influence de l'anemie aigue, Nevraxe **2** 2, 1900-1901

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10 Weinberger, L M, Gibbon, M H, and Gibbon, J H, Jr Temporary Arrest of the Circulation of the Central Nervous System, Arch Neurol & Psychiat **43** 615 (April) 1940

11 Ruge, A Kasuistscher Beitrag zur pathologischen Linsenkernerweichung bei CO Vergiftung, Ztschr f d ges Neurol u Psychiat **64** 45, 1922

12 Sayers, R R, and Davenport, S J Review of Carbon-Monoxide Poisoning, Public Health Bulletin 195, United States Treasury Department, Public Health Service, 1930

13 Ferraro, A Experimental Toxic Encephalomyelopathy Diffuse Sclerosis Following Subcutaneous Injection of Potassium Cyanide, Psychiatric Quart **7** 267, 1933

14 Hurst, E W Experimental Demyelination of the Central Nervous System, Australian J Exper Biol & M Sc **18** 201, 1940, **20** 297, 1942

15 Armstrong, H G, and Heim, J W Effect of Repeated Daily Exposures to Anoxemia, J Aviation Med **9** 92, 1938

16 Thorner, M W, and Lewy, F H The Effects of Repeated Anoxia on the Brain, J A M A **115** 1595 (Nov 9) 1940

17 Cohen, D J, Tannenbaum, A, Thalhimer, W, and Hastings, A B Influence of Oxygen and Carbon Dioxide on the Blood of Normal and Pneumonic Dogs, J Biol Chem **128** 109, 1939

18 Barach, A L, and Eckman, M A Mask Apparatus Which Provides High Oxygen Concentrations with Accurate Control of the Percentage of Oxygen in the Inspired Air and Without Accumulation of Carbon Dioxide, J Aviation Med **12** 39, 1941

19 Peters and Van Slyke,[4] 1932, vol 2, p 981

20 Horvath, S M, Consolazio, W V, and Dill, D B Syllabus of Methods of the Fatigue Laboratory of Harvard Business School, Harvard University, Cambridge, Mass, 1942

daily, except Sundays, were three to four hours in length and varied in number from 1 to 40 The oxygen content of the atmospheres ranged from 13 to about 4 5 per cent The atmosphere inspired was always at normal pressure

In addition to these dogs, the brains and spinal cords of 10 monkeys were studied These monkeys had been subjected, from 1 to 114 times, to daily anoxia in a decompression chamber Practically all the animals had been sent to a simulated altitude of 30,000 feet (9,000 meters), equivalent to a pressure of 225 mm of mercury, or an oxygen content of ± 6 per cent

One of the monkeys and 5 of the dogs were killed with ether All the other animals that did not die at altitude were killed by intravenous injection of pentobarbital sodium

The monkey brains and a few of the dog brains were fixed in toto Most of the dog brains, however, were blocked at autopsy, and pieces were placed in various fixatives, those most commonly used being solution of formaldehyde U S P diluted 1 to 10, 95 per cent alcohol, absolute alcohol and solution of formaldehyde U S P-bromide and solution of formaldehyde U S P-urea-potassium iodide fixatives The stains employed in varying degrees with the different animals were cresyl violet, hematoxylin and eosin, oil red O, and the Weigert-Van Gieson, Spielmeyer (or Weigert or Weil), Bielschowsky (or Bodian), Dockrill (oligodendroglia), Hortega (microglia), Cajal gold chloride-mercury bichloride, Holzer, Perdrau and Best carmine (glycogen) methods Occasionally the Eros, Pickworth or Alzheimer-Mann method was used

Blocks were taken from the frontal, parietal, temporal and occipital lobes and from the cerebellum, pons and medulla Usually sections of the whole brain were made from blocks cut according to Meynert's method at the level of the anterior and the posterior end of the hypothalamus, at about planes X and XV in the atlas of Winkler and Potter [21] A few spinal cords were likewise examined, both from dogs and monkeys The splanchnic nerve was also studied In addition, the adrenal glands were examined after being stained with the oil red O and the phenylhydrazine method [22]

The brains of 5 normal dogs and of 2 normal monkeys were prepared by the same technics as those used in the experiment, and these served as controls

PATHOLOGIC EXAMINATION

The brains of 25 dogs and 10 monkeys were examined The dogs had been exposed to low oxygen concentrations at normal, Boston atmospheric pressure, as previously described Ordinarily, an animal received a three to four hour exposure daily The monkeys were likewise exposed daily, but a decompression chamber was used, so that low pressure atmospheric oxygen produced the pathologic effect Since the lesions in the monkey brains were, to a certain extent, an accentuation of those found in the dog brains, the latter will be considered first

21 Winkler, C, and Potter, A An Anatomical Guide to Experimental Researches on the Cat's Brain, Amsterdam, W Versluys, 1914

22 Bennett, H S The Life History and Secretion of the Cells of the Adrenal Cortex of the Cat, Am J Anat **67** 151, 1940

DOGS

GROSS INSPECTION

Most of the dog brains presented no macroscopic abnormalities, they were not unusually injected, although the brain of 1 animal (Sophy) was strikingly pale, nor did they bulge or feel tense when the dura was opened Mild, fresh hemorrhage was sometimes observed over the base, but this almost invariably proved later to be unaccompanied with any reaction and occurred probably post mortem On section also there was but little abnormal to be seen The small hemorrhages so often reported with anoxia [23] were virtually never present On palpation, occasional small foci of softening were to be felt in the basal ganglia, usually bilaterally, and occasionally also in the subcortical white matter, particularly in the centrum semiovale, there were small, gray, rough patches These were not nearly so common in the dogs as they were in the monkeys, as will be described later

MICROSCOPIC EXAMINATION

The alterations that occurred in the brains may be roughly divided into two categories lesions in the gray matter and lesions in the white matter Each of these may be further subdivided into lesions of type 1 and lesions of type 2 The chief purpose in thus subdividing the histologic reactions encountered is convenience in description, although it is also true that certain of the reactions were characteristic in their location and type

Lesions of Gray Matter Type 1—What has been called the first type of lesion in the gray matter is really a combination of at least two types of changes in the nerve cells, together with whatever concomitant interstitial reaction there was These alterations have been grouped under one heading because they were the earliest and most consistent response which the brain made to this type of anoxia and because they were probably also, as will be pointed out later, at least partially reversible With the Nissl stain, the ganglion cells of the outer cortical layers were usually pale, chromatolytic, swollen and vacuolated These phenomena varied from one animal to another and sometimes from one region of the brain to another in the same animal The cells sometimes showed more swelling, chromatolysis and related changes than at other times, but the same type of response was found in practically all the brains, as can be seen in table 1 These ganglion cells were usually convex in outline (fig 1), with the nucleus eccentrically placed The cytoplasm was pale and contained a number of vacuoles, the interstices

23 Armstrong and Heim [15] Thorner and Lewy [16]

of which were colored by a fine, dusty, pulverized tigroid substance Sometimes these vacuoles were large, and three or four of them filled most of the perikaryon Often, however, they were much smaller, and fifteen or twenty of them could be seen in the section of one cell Usually, when the vacuoles were small the cell was rather dark and when they were large the cell was pale This vacuolation often extended out into the dendrites, as can be seen in figure 2, which shows a cell and its processes impregnated with silver Often the nucleus and the perikaryon

TABLE 1.—*Data on Dogs Exposed to Atmospheres Deficient in Oxygen*

Dog	Number of Experiments	Number of Days	Oxygen in Blood, Vol %	Lesion: Gray Matter Type 1	Gray Matter Type 2	White Matter Type 1	White Matter Type 2
Judith	25	33	13	+			
Duncan	33	44	12	+			
Pansy	10	11	11	+			
Lillian	28	38	10	+			
White Devil	29	60	10	+			
Snowball	5	8	9	+			
Casper	12	16	9	+	+	+	+
Allegra	44	61	8	+		+	
Oscar	4	8	8				
Horace	23	29	8	+			
Sadie	19	31	7	+		+	+
Timothy	16	20	6	+			+
Edwin	13	15	5.5	+			+
Patricia	63	71	5	+			
Harry	25	29	5	+			
Hector	25	28	5	+	+	+	+
Sophy	12	18	5	+			+
Wiener	7	11	5	+	+		
Puck	39	52	4.5	+		+	+
Jerry	36	43	4.5	+		+	+
Flora	35	42	4.5	+	+		
Genevieve	33	43	4.5	+			
Peter	12	46	4.5	+	+	+	+
Victor	11	22	4.5	+	+		+
Suzy	1	1	2.4				

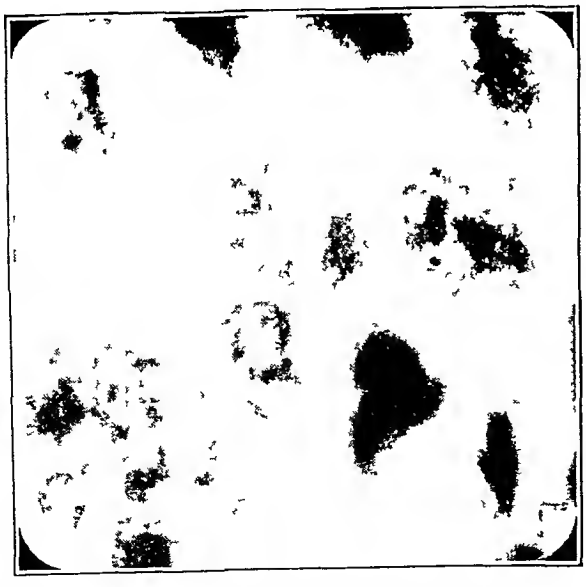

Fig 1 (dog Sophy).—Liquefaction necrosis in the outer cortical layers Nissl stain, × 400

close to the nucleus appeared relatively normal while the vacuoles around the outer margin of cytoplasm gave a fringed appearance to the edge of the cell The glial nuclei in the same regions were reduced in number, and the cytoplasm of the oligodendroglia cells and the astrocytes was vacuolated, as it was in the nerve cells In the Bielschowsky preparations, the neurofibrils passing through the perikaryon of these swollen, vacuolated cells were clumped and matted together and compressed to one side, or they extended like a cable through the depths of the cell close to the nucleus Usually they took the stain poorly and gave a stippled appearance In spite of the poor condition of the bodies of these swollen cells, the neurofibrils in the dendrites, especially in the apical dendrite, were well preserved

In sections stained with oil red O for fat no fatty degeneration was obvious but often after great care in adjusting the illumination a fine, dusty pink powder could be made out within the vacuoles

In addition to these cells of the supragranular layers in various parts of the cortex, the Purkinje cells exhibited swelling and vacuolation

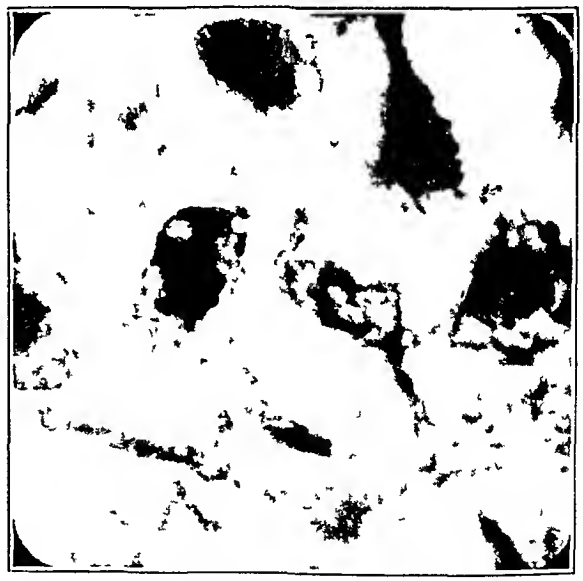

Fig 2 (dog Wiener).—Swelling and vacuolation of perikaryon even out into the processes Dockrill's silver stain, × 400

The vacuoles were arranged around the periphery of the cell, and the more central, perinuclear portion appeared relatively normal with well stained and orderly tigroid bodies (fig 4) No fat was present in these cells

Similar vacuolated cells, presenting varying degrees of chromatolysis sometimes accompanied with an increased number of satellites or undergoing actual neuronophagia were occasionally seen in the basal ganglia also Figure 5 shows such cells in the thalamus, where their condition more nearly resembled the "severe cell disease" of the German authors These cells,

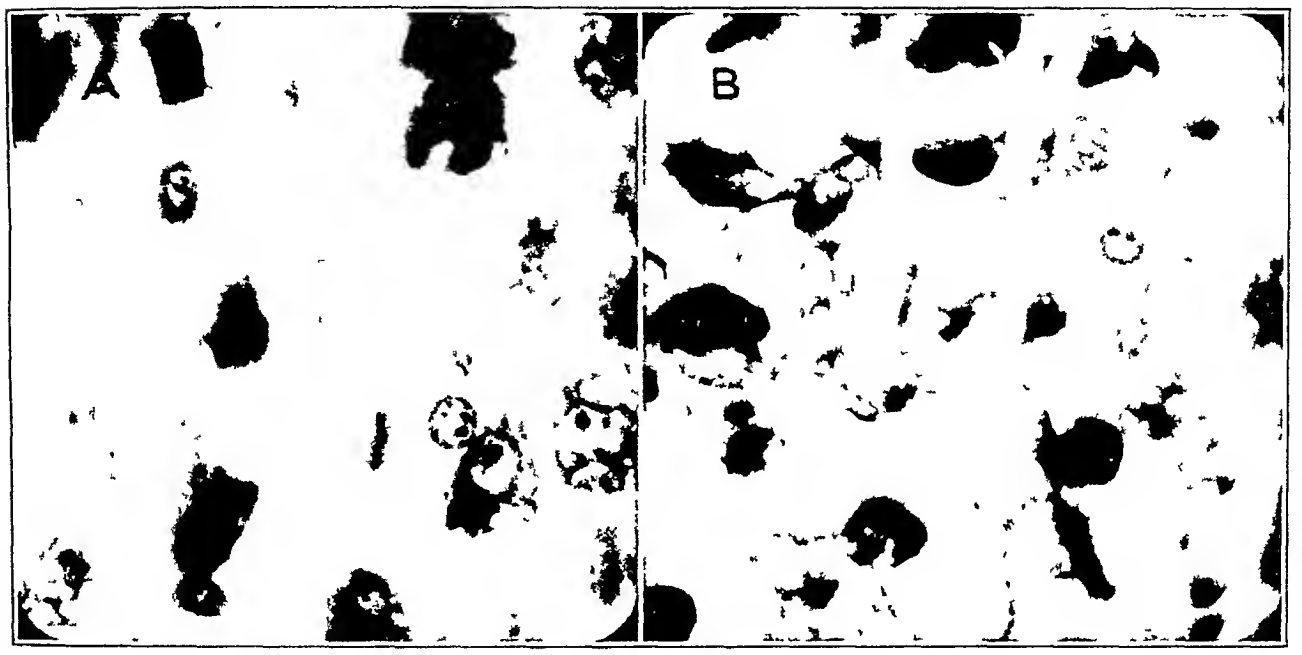

Fig 3—*A*, swelling and liquefaction of astrocytes among vacuolated nerve cells in the outer cortical layers Dockrill silver stain, × 400 *B*, swollen oligodendroglia cells among the vacuolated nerve cells in the outer cortical layers Dockrill silver stain, × 400

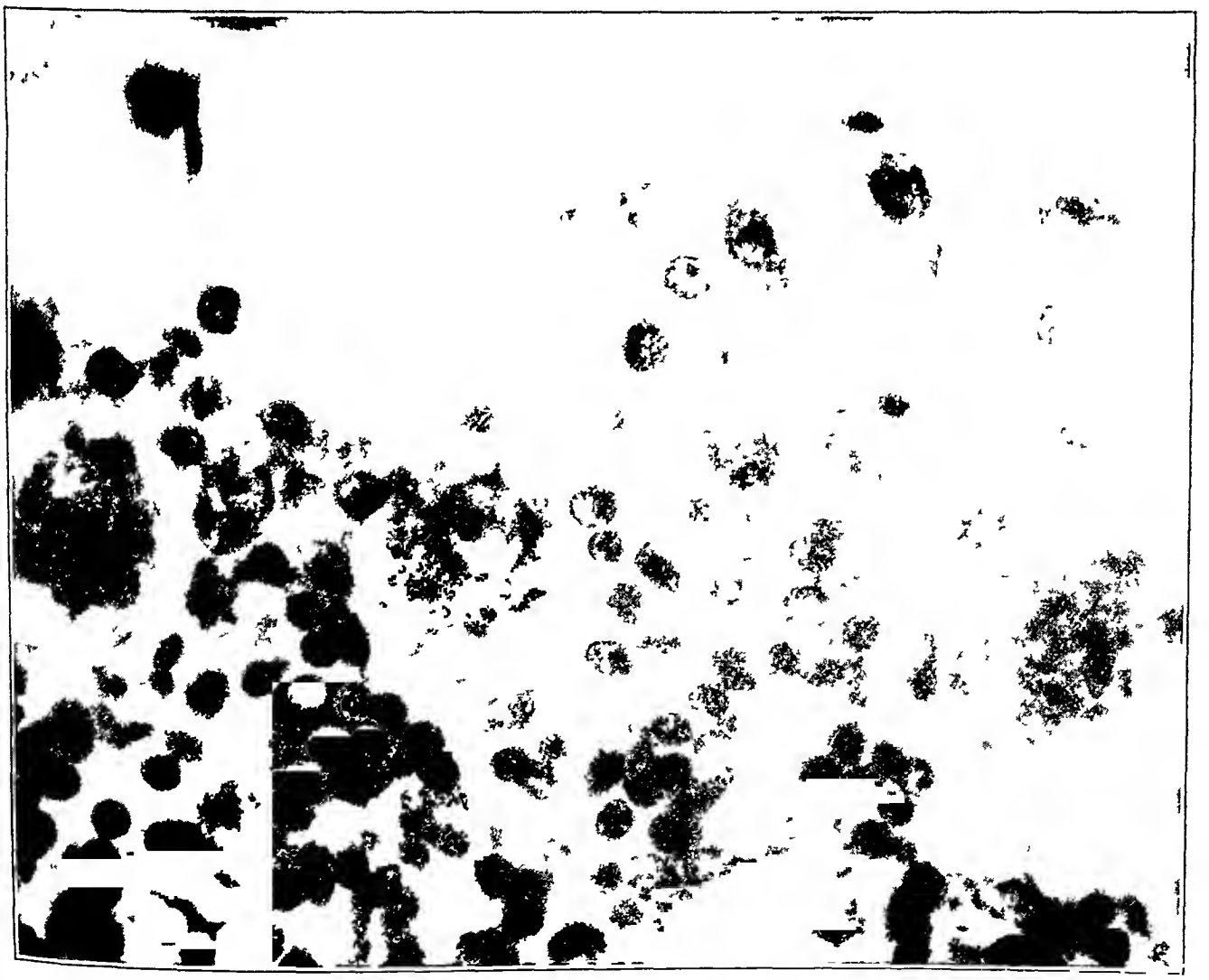

Fig 4 (dog Horace) —Swelling and vacuolation of the Purkinje cells Nissl stain, × 400

however were not very different from a lesion of type 2 to be described later

The difficulty in interpreting this type of reaction hinged on the fact that it was largely an exaggeration of the milder, less extensive change that is occasionally observed in the brains of normal dogs which have been prepared in the way these brains were In the control series were found cells that were vacuolated and chromatolytic to a slight degree, and when they were present in the controls they were located in the same general regions of the brain as in the experimental dogs, that is, in the supragranular layers of the cortex, and chiefly on the external surfaces of the gyri rather than in the depths of

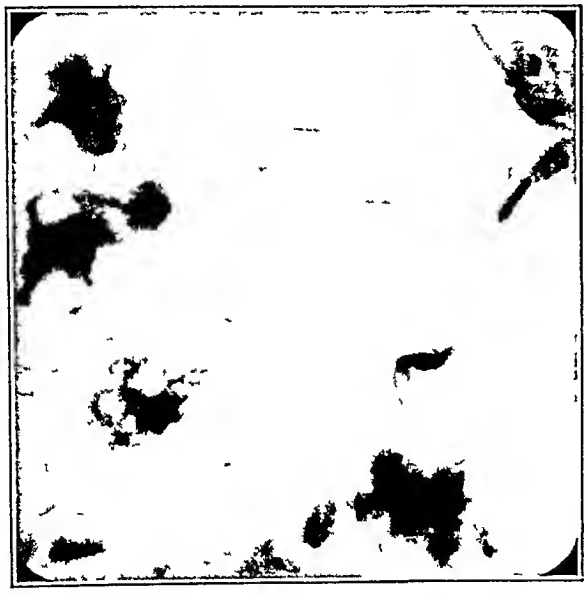

Fig 5 (dog Flora) —Chromatolysis and vacuolation of cells of the thalamus Nissl stain, × 400

the sulci This observation will be discussed in more detail later The remaining histologic alterations presented no such diagnostic problem

From the granular layer inward toward the subcortical white matter the chief ganglion cell disease was "shrinkage" Both ischemic and "chronic" shrinkage types were present, with the latter often more numerous and more conspicuous These shrunken cells in the deeper layers were sometimes present, as in dog Snowball, when no swollen vacuolated cells were present in the outer cortical layers The cells of the chronic shrinkage type (fig 6) were darkly stained, the cell bodies were elongated, with slightly concave surfaces, the processes were hyperchromatic throughout their extent, and the entire perikaryon was pyknotic The shrunken cell body, together with its apical dendrite, was often twisted into a corkscrew shape or otherwise distorted, and frequently such cells were surrounded by satellites (fig 7) When ischemic shrinkage types were present, all degrees of paleness were encountered, down to complete invisibility of the cells Sometimes several such cells would have disappeared in one spot, creating a minute acellular zone (fig 8), like Spielmeyer's *Herde* or the "pale areas" reported by Gildea and Cobb Long, sharp, hyperchromatic, spikelike processes were frequently found with these shrunken cells, like those reported in the work of Gildea and Cobb [6] These shrunken cells were scattered fairly densely among cells of a more normal nature, but in some regions of the cortex in certain cases entire zones were composed of cells of these shrunken types

With regard to the glia in these deeper cortical layers, it may be said that oligodendroglia cells were increased in number, occurring chiefly as satellites around diseased nerve cells—in contradistinction to the oligodendroglia cells normally found in the areas of "pseudoneuronophagia" [24] of the deepest cortical layers just overlying the white matter The increased satellitosis spoken of in this paper means the accumulation of glia

Fig 6 (dog Horace) —"Chronic shrinkage" in deeper cortical layers, with hyperchromatic, tortuous processes Nissl stain, × 400

cells around Betz cells or other definitely diseased cells which normally have no, or few, satellites (fig 27) Astrocytes also presented certain signs of hyperplasia, often becoming enlarged, containing two nuclei or being in the process of division, with paired daughter cells frequently seen With Cajal's gold chloride-mercury bichloride stain the processes were often thick and extensive, but Holzer preparations showed no gliosis (fig 9) The microglia

24 Spielmeyer, W Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p 493

cells were inconspicuous As gitter cells laden with fat they were present in a meager, scattered sort of way in the perivascular spaces and lying free in the parenchyma In addition to this, in Nissl preparations hyperchromatosis of microglia cells with polymorphic nuclei was seen fairly often, but unless there was more severe damage than has previously been described, even this low degree of activation of the microglia was scattered, isolated and insignificant

The blood vessels, except in certain specific conditions, to be described later, presented a moderate amount of thickening, characterized by endothelial and adventitial proliferation The adventitial overgrowth, seen best in the Perdrau preparations, was confined chiefly to capillaries, but the endothelial hyperplasia was seen better in the smaller arteries and veins The perivascular spaces were fairly widely dilated and presented a spongy, reticulated appearance This dilatation extended inward to about the same depth as did the swollen, vacuolated cells

Summary This first type of lesion in the gray matter fell short of true necrosis The ganglion cells in the supragranular layers were usually swollen, vacuolated and chromatolytic, and the glial changes were regressive In the deeper layers the cells were shrunken, pyknotic and hyperchromatic, with tortuous or spikelike processes, and were often accompanied with increased glial satellites The microglia cells were not conspicuous

Lesions of Gray Matter Type 2—Fewer than half the dogs presented this second type of lesion, as a glance at table 1 will show Most of the dogs that were repeatedly exposed to atmospheres with the lower oxygen percentages, and some dogs not exposed to such severe anoxia exhibited this type of reaction It was found in the cortex or in the basal ganglia, chiefly the thalamus, but was not seen in the medulla, the pons or the cerebellum These lesions were not all of the same age, so the microscopic picture varied from one animal to another In the earliest lesions there might be thickening of the vascular walls, with the endothelial nuclei of a longitudinally cut vessel touching one another in the Nissl or the hematoxylin and eosin preparations, while the Perdrau stain would show hyperplasia of vascular reticulum Van Gieson preparations showed no collagen over-

Fig 7—Severe "chronic shrinkage" with neuronophagia in the infragranular layers Nissl stain, × 400

growth Sometimes the perivascular spaces were cuffed with hematogenous cells, chiefly lymphocytes (fig 10), but this was not a frequent feature, and when it did occur it was in the more central portion of such a lesion, the vessels on the edge being merely thickened In the parenchyma itself in such a focus the ganglion cells might be chromatolytic and pale, although occasionally dark-staining cells were found, and they might be accompanied with an increased number of satellites, which in some cases had begun to invade the region of the disappearing cell body The oligodendroglial nuclei were pyknotic with the Nissl stain, and in the Dockrill preparations their processes rarely and the perikaryon readily took the Nissl stain and appeared as a pale, bushy fringe, conforming to the shape of the nucleus These microglia cells not only occupied the space among the ganglion cells but constituted the chief component of the glia participating in satellitosis and neuronophagia In such a lesion there was often a paling of the myelin, but no fat was present in the earliest stages The neurofibrils in such a focus were virtually intact

As these foci of incomplete necrosis advanced in age, all the elements involved underwent further change, either progressive or degenerative, In the Nissl preparations, the blood vessels were observed to continue their hyperplastic trend,

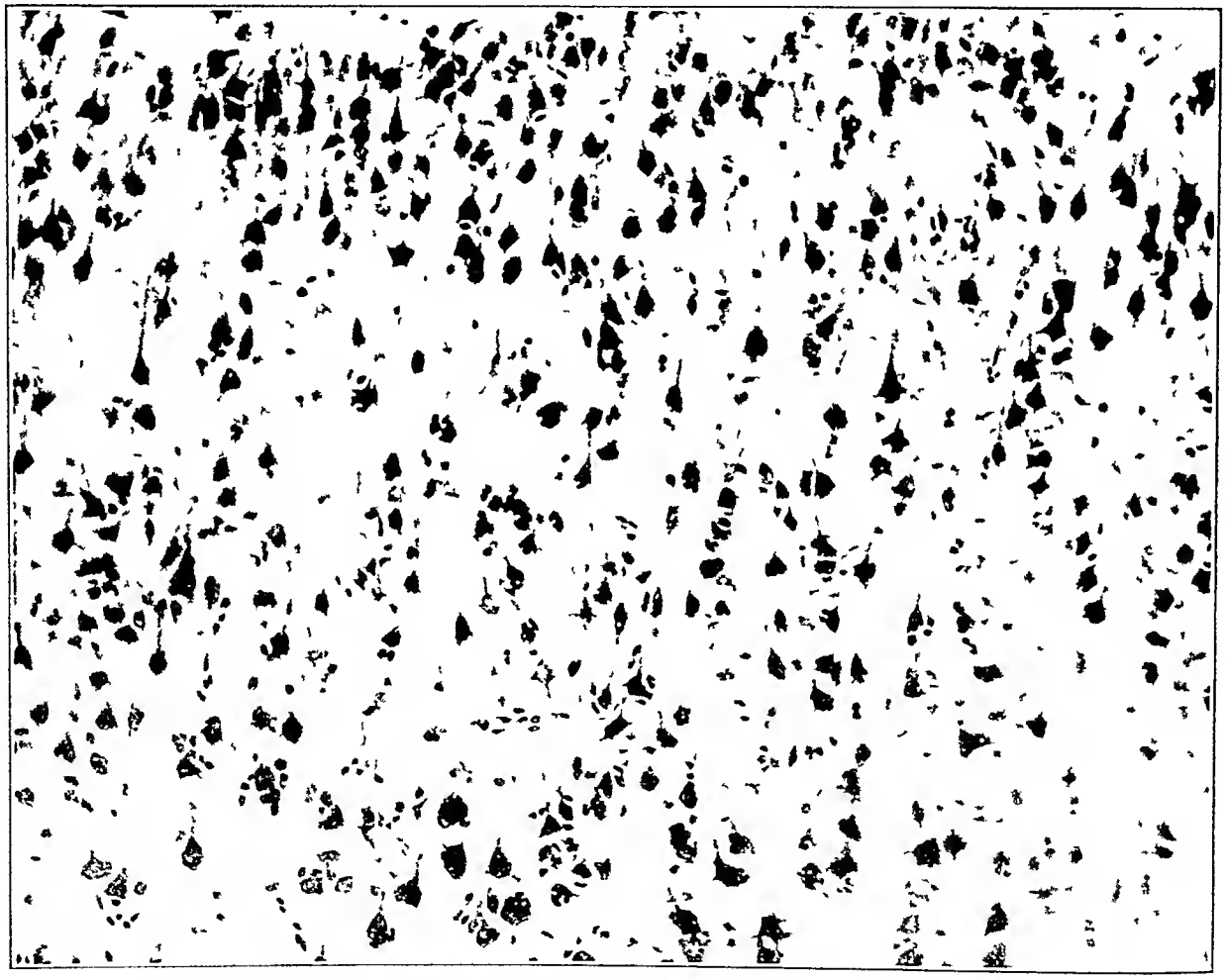

Fig 8 (dog Casper) —Minute acellular foci in the cortex Nissl stain, × 100

took the silver stain, although at the periphery of the lesion swollen oligodendroglia cells were common In these early foci astrocytes were inconspicuous, and with the Nissl stain their nuclei were often visible but practically always pale and disintegrating, as though undergoing lysis The cells that attracted immediate attention were the microgliocytes The entire zone might be closely packed with them In the early lesion which is being described their nuclei were hyperchromatic, hypertrophied and pleomorphic, with thickening of the walls, budding of endothelial cells and formation of new blood vessels They lost any cuffing of hematogenous cells they might have had and were often surrounded instead by compound granular corpuscles Most of the ganglion cells had completely disappeared, but the remaining ones often appeared fairly normal The oligodendroglia cells in the depths of the focus, and the astrocytes as well, were reduced to occasional pyknotic nuclei or were entirely absent The microglia cells might

be in any stage of activity, from the polymorphonuclear type to the gitter cell, and sometimes the entire focus would be made up of the latter (fig 11) The myelin in such a spot was now

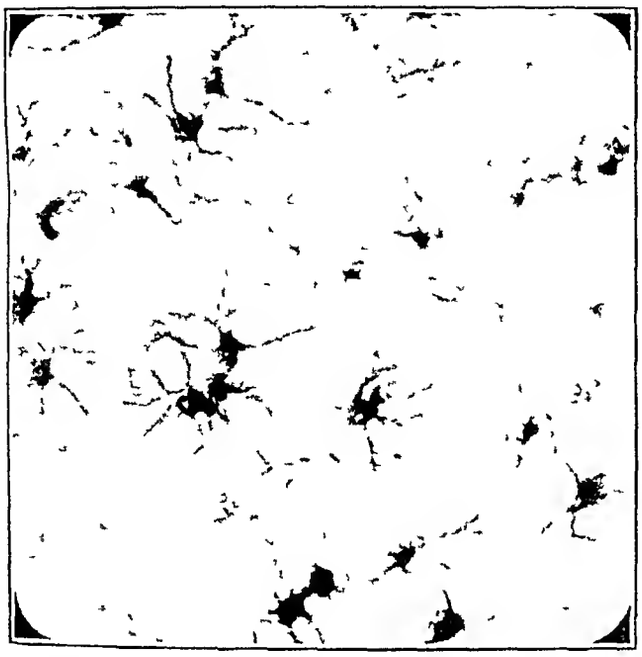

Fig 9 (dog Terry) —Slight astrocytic hyperplasia in deep cortical layers Dividing astrocytes were fairly common, but fibrous gliosis was scanty Cajal's gold chloride-mercury bichloride, × 100

broken down, and in the oil red O preparation neutral fat was visible everywhere, the granular corpuscles being laden with it, not only in the

Fig 10 (dog Hector) — Perivascular cuffing with hematogenous cells, chiefly lymphocytes, in the thalamus Nissl stain, × 100

perivascular spaces but throughout the parenchyma With this stain the vascular endothelium, also, was seen to be well filled with bright red fat droplets (fig 12) The Spielmeyer or the Weil stain showed loss of myelin, varying from mild to total, while the neuro-

fibrils, although presenting thickenings and tumefactions, were often retained in relatively good condition The astrocytes in such a focus, when seen in a Cajal preparation, showed occasional feeble attempts at hyperplasia, daughter cells being seen at the periphery of the lesions, but in general the cell bodies, and the processes as well, were granular or fragmented, and in the

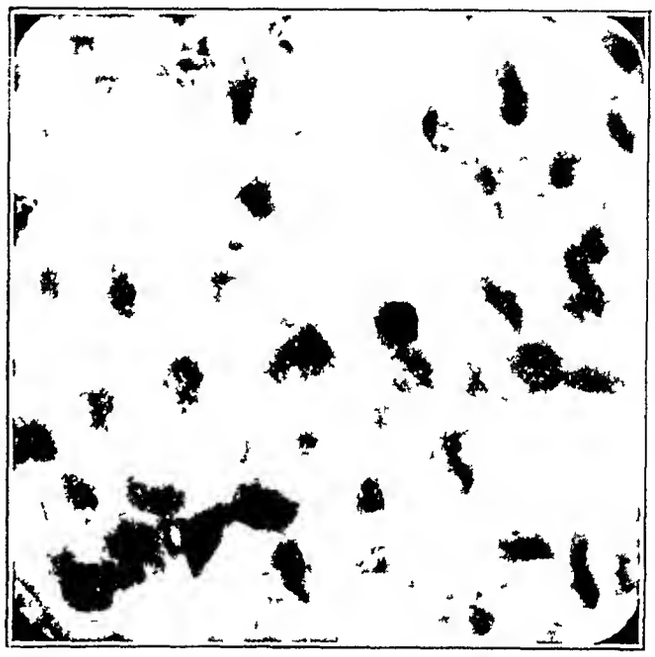

Fig 11 (dog Flora) —Compound agranular corpuscles in a necrotic focus in the thalamus Nissl stain, × 400

depths of the focus the astrocytes were absent Of course, there was no reaction to the Holzer stain

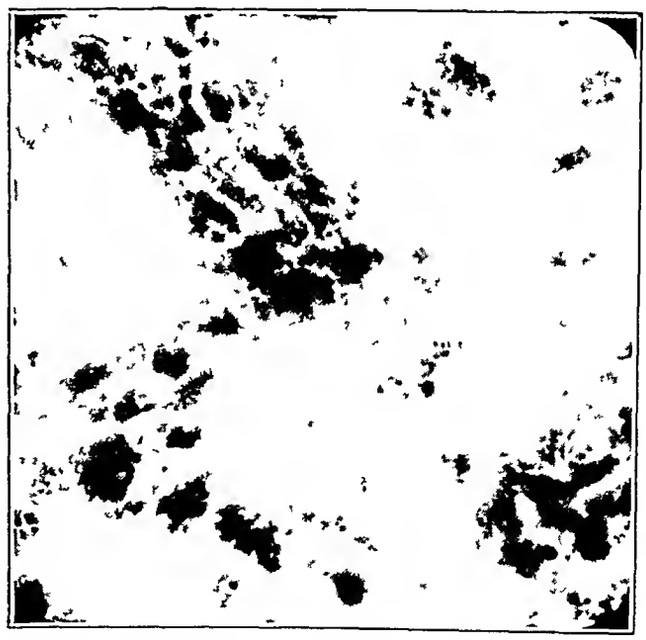

Fig 12 (dog Hector) —Fat-laden gitter cells, as well as fat, in vascular fibroblasts Oil red O stain, × 300

Summary The second type of lesion of the gray matter consisted in various degrees of necrosis, marked by loss of nerve cells through lysis or neuronophagia, thickening of vascular walls, hyperplasia of microglia cells, fatty ne-

crosis of myelin, perivascular cuffing with hematogenous cells and formation of gitter cells

Lesions of White Matter Type 1.—The lesions of the white matter have also been subdivided, for purposes of description, into two groups, but this subdivision is rather arbitrary, and three groups might have been named instead of two, or perhaps all three might have been included under one head and described as different stages of one type of lesion as seen with different stains This possible relation will be considered in the subsequent discussion What has been called the type 1 lesion consisted in macroscopic pallor of the white matter as seen with the Weigert, Weil or Spielmeyer stain The lesions were found almost entirely in the subcortical white matter, and most commonly in the centrum semiovale (fig 13) The corpus callosum was often involved also, but the central fingers of myelin which extended into the gyri, especially those from the centrum semiovale, were the chief foci of involvement The temporal lobe was less commonly affected than the frontal, parietal and occipital lobes The cerebellum was not a usual site of attack, but in 1 case, for example, in which the lesions did strike there they were extensive (fig 14) These lesions of type 1 were seen to better advantage in the monkeys than in the dogs, but the earlier stages were found most often in the latter At times the lesions were perivascular, and at other times any connection with blood vessels was not obvious The blanching of the myelin sheath as shown with Weil's stain was often unaccompanied with any neutral fat in the sections stained with oil red O, and in

Fig 13 (dog Terry) —Loss of myelin in the subcortical white matter, centrum semiovale and corpus callosum Modified Weil stain, × 4

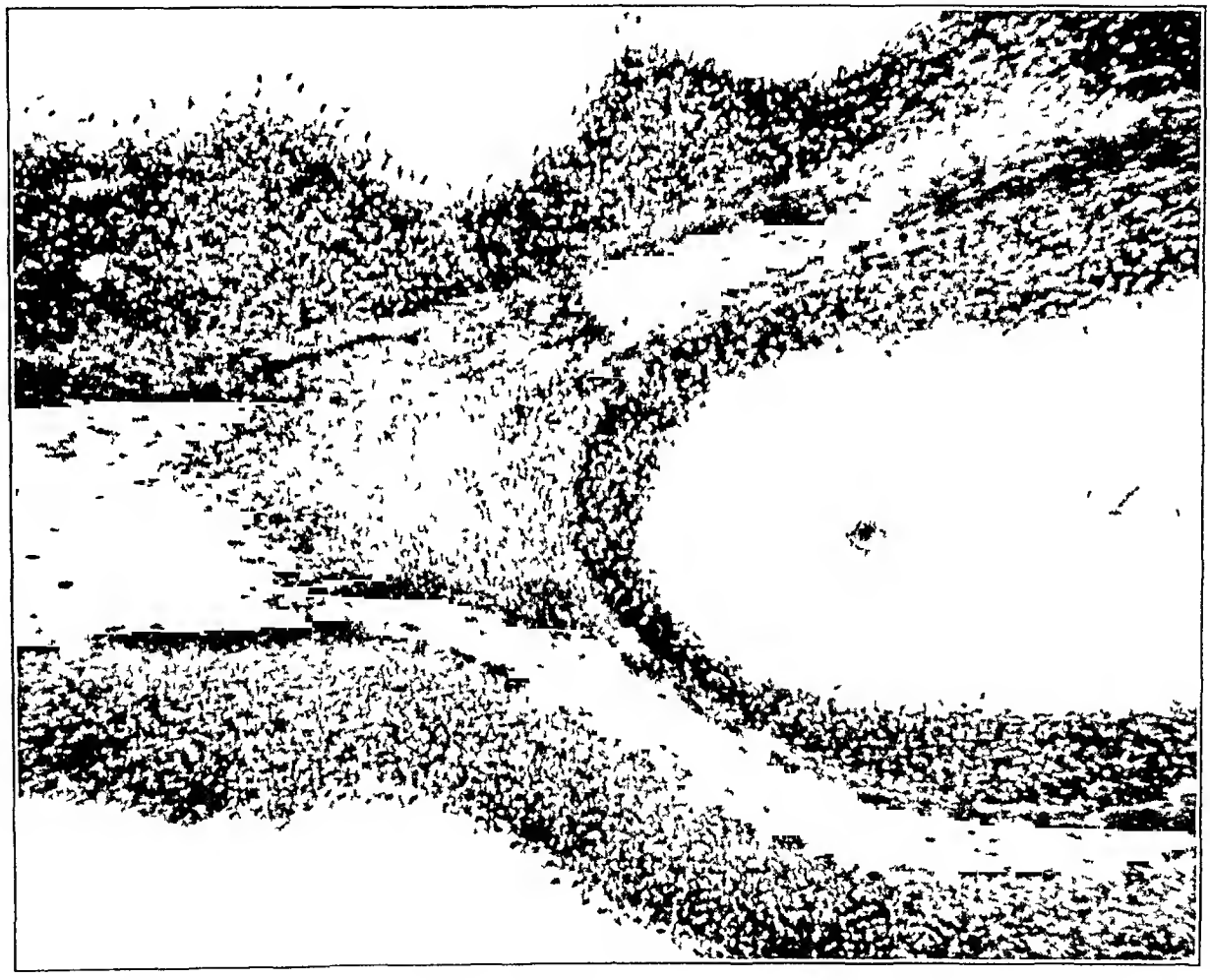

Fig 14 (dog White Devil) —Small focus of demyelination, part of a more extensive lesion, in the cerebellar white matter Weigert stain, × 30

polarized light there was still double refraction in most places Examination with a high power lens revealed swollen sheaths in the depths of the lesion, accompanied with myelin figures, but toward the edge of the lesion the sheaths appeared merely pale, without any irregularities This indicates that the lesion was usually slightly older at the center than at the edge, indeed, when the lesion was more advanced in age than that which has just been described, fat was present in the central portion before it appeared at the edge This observation will be mentioned again

poral lobe and in the cerebellum They were not seen in the medulla or the spinal cord

The usual appearance with the Nissl stain (fig 15) was a reaction of interstitial cells in the subcortical white matter A cluster of blood vessels with thickened walls might be surrounded by a field of hyperplastic microglia cells with pleomorphic nuclei, forming fairly dense collars about the individual vessels and gradually diminishing in numbers and in degree of activation until normal fields were reached at the periphery of the focus The picture was not always the same because the age of the lesions varied from

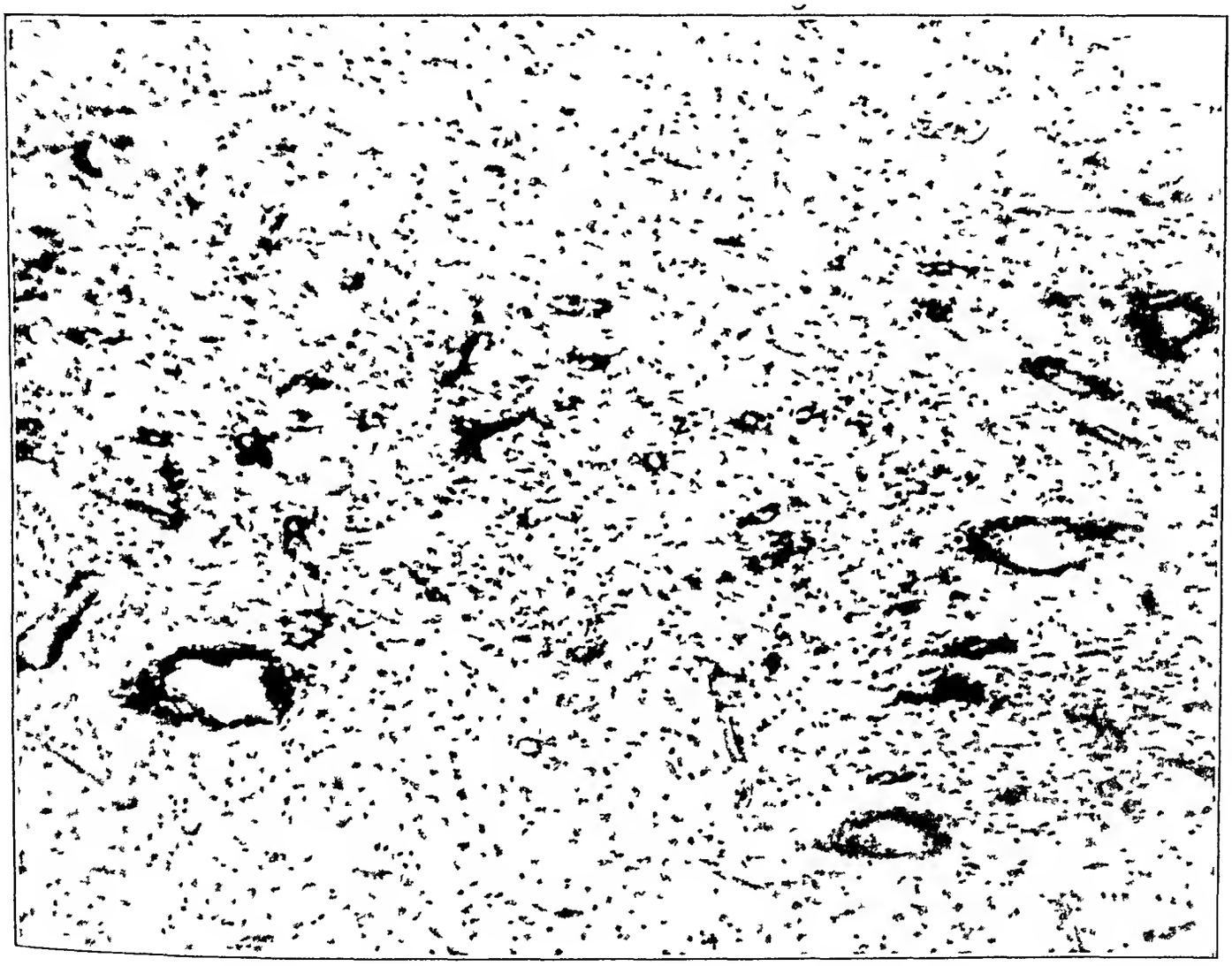

Fig 15 (dog Peter) —Typical focus in the centrum semiovale, with thickened blood vessel walls in the midst of pronounced microglial hyperplasia The overcellularity throughout the field consists in hyperplasia of microglia cells with pleomorphic nuclei Nissl stain, × 100

Lesions of White Matter Type 2 —The cellular reaction is the chief feature of this type of lesion, and, as previously mentioned, it is intimately associated with the demyelination of the first type of lesion of the white matter, which is characterized by pallor The site of the lesions was the same as that of the type 1 lesions, namely, in the subcortical white matter of the various convolutions, and especially in the centrum semiovale Such lesions occurred in all lobes of the brain, but less frequently in the tem-

one animal to another, although the age was probably always about the same in different regions of the brain in any one animal There might be hematogenous cells in the perivascular cuffing, consisting chiefly of lymphocytes but occasionally of a few polymorphonuclear leukocytes At a later stage compound granular corpuscles might be found in the Virchow-Robin space or in the parenchyma beyond The hematogenous cells were never seen in the parenchymatous tissue Among the hyperplastic microg-

lia cells, plump astrocytes, *"gemastete* cells," were sometimes present (fig 16) The walls of the blood vessels varied in thickness from normal capillaries with a single row of endothelial cells to those with endothelium four or five rows thick Longitudinally cut vessels might show endothelial nuclei touching one another, and even piling up in greater numbers Often the vessel looked thicker in sections stained with the Nissl method than the number of endothelial nuclei would warrant, in such cases the Perdrau stain showed a dense overgrowth of reticulin, while the Van Gieson stain did not show much in-

Fig 16 (dog Peter) —Plump astrocytes (*A*) among the microglia cells (*M*) Nissl stain, × 300

crease in collagen In the Nissl or Dockrill preparations long rows of oligodendroglia cells (fig 17) were often found along these capillaries, and other small vessels, when they were cut longitudinally, and when similar vessels were stained with Perdrau's method, hyperplasia of the reticulin was encountered This will be discussed later

As regards the relation of these cells to the structures they lie among, it was seen with the stain for fat that the great majority of these polymorphonuclear microglia cells contained no fat in their cytoplasm Of all the forms of glia cells only the full-fledged gitter cells, lying chiefly in the perivascular spaces, or close to them, contained fat In addition, the endothelial cells of the blood vessels were often stippled with granules of neutral fat Even though the Weil stain showed paling of the myelin in the neighborhood of such a zone, as has previously been mentioned, the amount of the fat in these early lesions was extremely meager Furthermore, it was often noticed that the gitter cells scattered free in the tissue were of conspicuous size but only a pale straw color, rather than bright red, with the oil red O stain With crossed Polaroid these gitter cells were seen to contain material that was still anisotropic The nuclei were indistinguishable from the microglial nuclei of ordinary compound granular corpuscles [25] Some of the axons passing through this hypercellular zone became thickened, but no severe destruction of axons was present in these early lesions, and practically no signs of axonal reaction could be detected in the neighboring cortical cells

The sequence of development of these lesions was as follows alteration of the myelin, hyperplasia of microglia accompanied with perivascular collections of lymphocytes and polymorphonuclear cells, thickening of walls of blood vessels development of gitter cells, recession of hematogenous cells fatty degeneration of myelin degenerative changes in oligodendroglia cells and in some astrocytes, hypertrophy of other

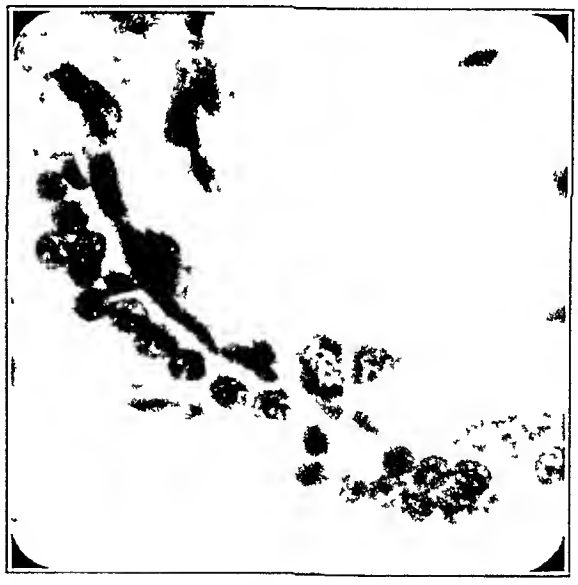

Fig 17 (dog Peter) —Rows of perivascular oligodendroglia cells, often present in white matter and sometimes in gray matter as well Nissl stain, × 400

astrocytes and swelling of neurofibrils This sequence will be discussed later, and possible explanations for apparent differences in the order of events will be presented

MONKEYS [26]

GROSS INSPECTION

The 10 monkeys in this study ranged in age from 2 to 4 years and weighed on an average

25 Hassin, G B Histopathology of the Peripheral and Central Nervous Systems, New York, Paul B Hoeber, Inc, 1940, p 554

26 Nine of the monkeys whose brains and spinal cords were studied here were observed during experi-

about 4,500 Gm The weight of the brain was about 90 Gm Table 2 gives details concerning the altitude reached and the number of exposures experienced by each animal, as well as the mode of death Few of the animals presented any abnormal signs, but the clinical data on 2 of them deserve mention Animal P67 showed

TABLE 2—*Data on Ten Monkeys Exposed to Daily Anoxia in Decompression Chamber*

Monkey No	Number of Experiments	Number of Days	Oxygen, %*	Lesion: Gray Matter Type 1	Gray Matter Type 2	White Matter Type 1	White Matter Type 2
P61	5	5	7				
P64	5	5	7	±		+	
P65	15	15	6	±			
P66	40	40	6	+		±	+
P67†	47	47	6	+	+	+++	+
P78	96	96	6	+		+++	++
P80†	112	112	6	±	+	+	+
P81†	112	112	6	±		+++	±
P82†	114	114	6	+	±	++	+++
1633	1	1	6		+++		

* Animal breathed room air at a pressure of 275 or 225 mm of mercury
† Animal was killed with pentobarbital sodium

marked weakness of the hindlegs after each daily exposure There was apparently complete recovery in about an hour, and no residual signs could be elicited The brain presented no abnormal features on inspection with the naked eye Animal P82 on one occasion two months before death had a right-sided epileptiform convulsion The brain appeared normal except for a pale yellow, shallow depression in the occipital lobe, running in a coronal plane midway between the sulcus lunatus and the tip of the lobe, and a second, smaller, depression on the superior margin of the postcentral gyrus These regions felt soft to the touch The other animals showed no abnormal conduct during the experiments The brain of monkey P80 presented a yellow, depressed streak on the left postcentral gyrus, extending out into the superior parietal gyrus The brain of monkey P66 presented unusual engorgement of the pial vessels On section, several of the brains exhibited grayish, slightly roughened patches in the region of the centrum semiovale, otherwise, nothing remarkable was noted

MICROSCOPIC EXAMINATION

The same division of lesions into types occurring in the gray matter and types occurring in the white matter obtained with the monkeys as with the dogs In the monkeys, however, the changes in the gray matter were less pronounced, while the alterations in the white matter were more pronounced, than in the dogs

Lesions of Gray Matter Type 1—The combination of alterations in the nerve cells characteristic of this type was found to some extent in every case In the supragranular layers the vacuolation was of a slightly different character from that seen in the dogs in that the vacuoles were usually smaller and more closely crowded about the edge of the cell The chromatin, instead of being vitreous in appearance, might be darkly stained, and the nucleus was usually pyknotic There was but little glial accompaniment These vacuolated cells were not universally distributed in the supragranular layers but occurred in clusters or in zones Sometimes in one section most of the cells of the outer layers of an entire gyrus might be affected, while neighboring convolutions showed relatively few vacuolated cells Then, too, in the deeper layers this vacuolated type of change was sometimes encountered in single cells or in small groups of cells, but here the reaction was apt to be of a more advanced nature Betz cells, for example, might have the vacuolation of cytoplasm, the streakiness of chromatin and the satellitosis characteristic of severe cell disease These scattered, vacuolated cells of the deeper layers were found among the shrunken cells so commonly seen in these brains Extremely concave bodies, sometimes pale and sometimes deeply stained, with corkscrew processes in some instances and spikelike processes in others, and with the nucleus often eccentrically placed and pyknotic, characterized these shrunken cells Sometimes they were accompanied with oligodendroglial or microglial nuclei Pale areas caused by lysis of small groups of cells did not seem as common in the monkeys as in the dogs, although there were in all cases scattered ghost cells so pale as to be scarcely visible In the cerebellum, in the majority of cases, long rows of Purkinje cells frequently showed large vacuoles around the periphery, with the rest of the cell in fairly good condition, though perhaps slightly hyperchromatic Sometimes, however, rows of skrunken, pyknotic, hyperchromatic cells with overstained processes were visible The granular cells were not noticeably affected

ments under lowered barometric pressure in a decompression chamber in the laboratory of the Aviation Medicine Unit, Division of Industrial Hygiene, National Institute of Health, United States Public Health Service, Bethesda, Md The material was furnished through Surgeon Benjamin F Jones, United States Public Health Service, and Dr Frederic D Chapman, formerly Assistant Surgeon (R), United States Public Health Service Their physiologic observations have not yet been published, although some have been reported to the Committee on Aviation Medicine of the National Research Council The other monkey brain (1633) came from the department of physiology at Yale University, through Dr John Fulton

Lesions of Gray Matter Type 2.—This type of lesion was virtually nonexistent in most of the monkeys of the P series. The only animals of this group to show this severe type of reaction in the cortex were monkeys P80 and P82. The former had a severe lesion in the left postcentral gyrus and the latter a lesion in the left occipital lobe. In addition, monkey P67 presented a small lesion in the thalamus. While these lesions were distinctly different from the lesion of type 1, just described, they were not quite identical with the lesions of type 2 in the gray matter of the dogs. In the dogs the pathologic process was more nearly that of incomplete necrosis, while in the monkeys typical foci of softening were encountered in the gray matter. But all these changes were, to some extent, relative. The ganglion cells were destroyed along with the myelin sheaths, axons, oligodendroglia cells, astrocytes and even blood vessels. The intensity of changes in the lesion diminished toward the periphery, the focus being closely packed with fat-laden gitter cells in the deeper portions and only moderately so farther out. In the relatively sound tissue beyond the zone of granular corpuscles, ameboid astrocytes were in profusion, giving a clue to the age of the lesion. Practically no fibroblastic proliferation was encountered. These lesions were entirely cortical in extent and included virtually the entire depth of the gray matter at their greatest penetration, shading off gradually, so that at the periphery only the outer molecular layer was involved. No such lesions were found in the basal ganglia.

Incomplete necrosis of the gray matter was found in another animal. Macacus monkey 1633 is described separately because the microscopic picture was unique in the series, although practically identical with that of lesions in human brains described by other investigators,[27] an observation which will be discussed later. This animal was subjected to standard progressive decompression, the pressure reaching that at a simulated altitude of about 32,500 feet (10,600 meters), or 200 mm. of mercury, in twenty-three minutes. On recompression, several minutes of artificial respiration was necessary. When let loose in the runway, the animal appeared slug-

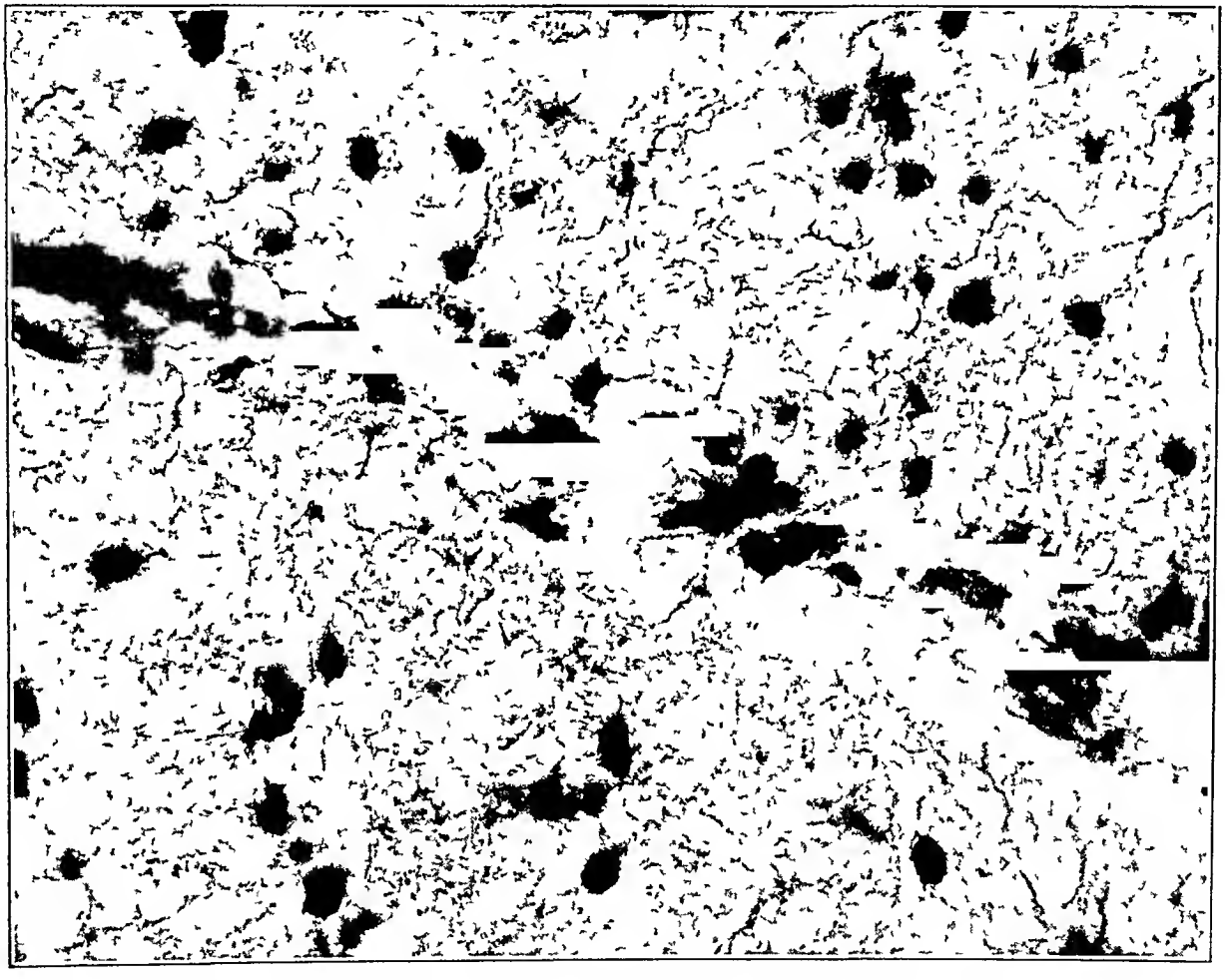

Fig. 18 (dog Flora).—Long rows of perivascular oligodendroglia cells. Dockrill stain, × 400.

27 Stewart, J. D. Cerebral Asphyxia During Nitrous-Oxide and Oxygen Anesthesia, New England J. Med. **218** 754, 1938. Courville.[5]

gish ataxic and weak on the right side and showed slight forced grasping in both forelimbs and hindlimbs The animal improved during observation but eight days later it was seen to climb slowly, use its fingers poorly and drag the fingers of the right hand when walking The next day nine days after the decompression, the animal was killed with ether

Postmortem examination showed the brain to be under increased intracranial pressure The microscopic lesions were extensive They were confined almost exclusively to the gray matter, being most often present in the third, fourth and fifth cortical layers in the frontal, parietal and occipital lobes The temporal lobes were singularly free from disease, as were the pons, cerebellum and medulla There was a well circumscribed focus in the globus pallidus

The Nissl stain showed dense thickening of the blood vessel walls, with increased cellularity of the endothelium, adventitial hypertrophy and formation of new capillaries The nerve cells were severely affected, over half of them being destroyed in any region which was involved Swelling chromatolysis and vacuolation of the cell body, with eccentricity and swelling of the nucleus, extensive satellitosis and neuronophagia, were commonly observed Compound granular corpuscles were abundant throughout the affected fields, while astrocytes and oligodendroglia cells showed regressive changes Clusters of microglia cells with rod-shaped nuclei were seen in the less severely affected zones, and nodules of oligodendroglia cells were frequently found in the sites of former nerve cells In the myelin preparations the most striking lesions were seen Extensive, patchy demyelination, in the form of "moth-eaten" spots, throughout the three affected layers was the usual change observed Figure 19 shows such a patch, with interruption of the fan fibers passing through the diseased zone The oil red O stain showed that this region was filled with fat, broken-down myelin sheaths, fat-laden gitter cells and astrocytes and nerve cells undergoing fatty degeneration Fatty degeneration of the nerve cells was not so extensive as might have been expected from the severity of the lesion as seen with the Nissl and myelin stains Bodian silver preparations showed many intact, normal axons traversing the affected zones, although most of them had become granular and fragmented Swelling and thickening

Fig 19 (monkey 1633) —Extensive laminar seminecrosis, with loss of fan fibers in the cortex Spielmeyer stain, × 30

of axons were not common Hortega's stain for microglia showed all stages of development of gitter cells, as well as small clusters of rod cells ("glial bushes") There was no Holzer reaction, and the amount of collagenous hyperplasia was limited, but Perdrau's stain (fig 20) showed dense hyperplasia of reticulin in the adventitia of vessels in the zones of the lesion The thickened walls of blood vessels and the formation of new vessels in the midst of a zone of semnecrosis presented the appearance of what Courville [5] described as an "astrovascular scar," al-

Fig 20 (monkey 1633) —Hyperplasia of the reticulin Perdrau stain, × 400

though proliferating astrocytes were certainly not present in this case and it is difficult to tell from Courville's illustrations that they were present in his cases

Lesion of White Matter Type 1 —The most obvious lesion of the entire series was the macroscopic blanching of the tongues of subcortical white matter as they extended into the various gyri, as seen with the Weil stain (fig 21) As table 2 shows, the first 3 monkeys, none of which had more than 15 exposures, did not present this lesion, but all the animals that received 40 or more exposures were affected The disease extended from the frontal to the occipital pole, with perhaps slightly less involvement of the temporal than of other regions of the brain The cerebellum was occasionally involved Secondary degeneration of the pyramidal tracts could be followed into the spinal cord As in the dogs, the centrum semiovale was the site of predilection with involvement of the neighboring subcortical marrow, as well as the corpus callosum The lesion tended to conform in shape to the shape of the mass of white matter in which it was situated, being long and narrow where the white matter was long and narrow, broad and fan shaped where the white matter was broad and fan shaped and triangular where the white matter was triangular The lesions were invariably located in the more central regions of the white matter, leaving at all times a rim of relatively intact myelin between the diseased tissue and the normal gray matter It is pointed out that this distribution is reminiscent of Schilder's disease (progressive subcortical encephalopathy), and this point will be discussed later in connection with other types of anoxia [28]

Microscopically the appearance varied somewhat with the age of the lesion, and, while this differed in different animals, it is emphasized that in any one animal the lesions were nearly always of the same age whether in the frontal, the parietal or the occipital zone In the early lesions, especially those which were invisible to the naked eye with the Weil or the Spielmeyer stain, swelling and paling of individual myelin sheaths, some of them with vacuolations and balloonings, were probably the first signs It is not possible to be categoric on this point because of the character of the cellular reaction, which will be described under lesions of type 2 At first the number of pale sheaths was so slight that they could easily be overlooked Later, as the disease of the myelin increased in severity, patches of obvious demyelination developed These consisted of pale, thickened sheaths, swollen irregularly into great vacuolated tumefactions and interlacing with one another so that a fenestrated appearance was given to the affected zone Fragmentation of some sheaths resulted in glistening *Marchballen* lying among the diseased sheaths With the oil red O stain no fat would be found at this stage of degeneration With polarized light the Marchi balls were doubly refractile, as were the myelin sheaths themselves (fig 26) As the age of the lesion increased, the demyelination progressed and was usually

28 Ferraro [13] Hurst [14]

most intense in the central zone, fading out gradually to normal tissue at the periphery Sometimes a blood vessel was located near the most intensely demyelinated part of the focus (fig 24) but often equally intensely demyelinated foci bore no apparent relationship to blood vessels Only extremely gradually did the myelin and other structures break down into neutral fat, and in the older lesions this fat was seen with the oil red O stain as bright red globules lying free in the tissue spaces in sparse distribution or engulfed in granular corpuscles which were by no means numerous except in the oldest lesions, or contained within the endothelium of blood vessels In a well developed lesion the gitter cells might be massed together, and in the neighborhood of the axons that must have passed through the affected zones in the centrum semiovale often showed marked swelling of the perikaryon, eccentricity of the nucleus and sometimes peripheral pyknosis But the conventional central chromatolysis of typical retrograde degeneration was rarely present Often, however, these affected Betz cells were accompanied with satellites, few or many, and occasionally they underwent neuronophagia (figs 27 and 28)

Lesions of this type were present in the cerebellum in only 2 monkeys, 1 of which showed but few and small foci, while the other exhibited extensive partial demyelination of the subcortical white matter throughout the cerebellar hemispheres

Fig 21 (monkey P67) —Demyelination and patchy loss of myelin in the centrum semiovale, corpus callosum and subcortical white matter Weil stain, × 4

sections stained with oil red O, such as those of monkey P66 (fig 31), in which a focus of fat-filled microglia cells occurred in the midst of an otherwise mild but extensive lesion, they appeared brilliant red Further discussion of the microglia is better left to the description of lesions of the white matter of type 2 The loss of myelin was accompanied with alterations in the axons Thickening of the latter, followed later by moniliform swellings, vacuolation, tortuosity and fragmentation, ending finally in complete destruction, was the usual course of events

With regard to the effect on the cortical nerve cells of this loss of myelin and destruction of axons, it may be said that advanced axonal reaction was but rarely observed However, examination of the Betz cells, for example, in

Secondary degeneration resulting from lesions in the centrum semiovale, corona radiata and like structures was traced into the spinal cord of the majority of the animals Pallor of the corticospinal tracts was visible on inspection with the naked eye of sections stained with the Weil method With the microscope, swollen sheaths and myelin figures could be seen in the pyramidal pathways

Lesion of White Matter Type 2 —In some cases this second type of reaction apparently preceded the demyelination In monkey P61 there was a slight focus in the centrum semiovale of the parietal lobe in relation to a small blood vessel In other circumstances, the lesion might have been passed over as one of the many minor variations of otherwise normal structure,

but being a collection of hyperplastic microglia cells similar to but smaller than, those to be described it assumed significance Animal P65 had a few such small foci, together with hyperplastic astrocytes, in the centrum semiovale and the corpus callosum It must be pointed out that in neither of these animals was the focus entirely typical of the lesions observed in the 6 animals next in the series, which had received greater numbers of exposures, although it somewhat resembled them

As in the dogs, the outstanding feature of these typical, and pathologic, foci was overcellularity, microglia cells, with polymorphic nuclei and bushy perikaryons, sometimes in relation to blood vessels and sometimes not, were found in the subcortical white matter In some of the lesions these collections of microglia cells were loose and scattered as in the dogs while in others they formed tight collars about blood vessels (fig 29) Most of these cells contained no fat The blood vessels themselves had thickened walls, all layers being involved in hyperplasia, although formation of new blood vessels was not observed The cells farther out from the perivascular cuffs were but loosely scattered and consisted not only of bizarre-shaped microglocytes but of many plump astrocytes, with

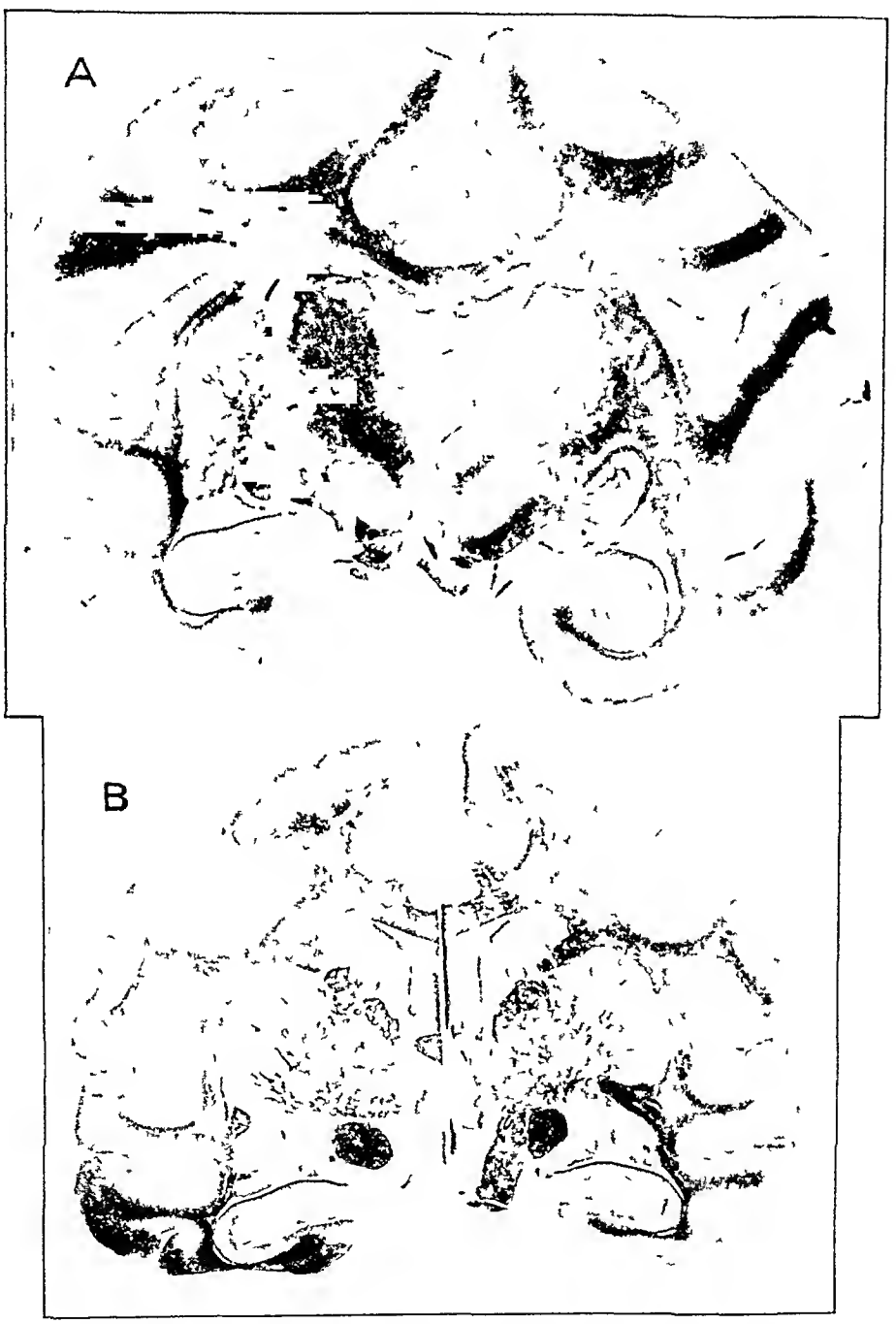

Fig 22—*A* (monkey P66), early loss of myelin and blanching of white matter in the centrum semiovale and in the temporal lobe *B* (monkey P82), more extensive loss of myelin Weil stain, × 4

their eccentric nuclei, their eosinophilic, homogeneous, waxlike cytoplasm and, in the Nissl preparations, their stubby processes (fig 30) In certain animals, as in the most severely affected monkey, P67, and in monkeys P66, P78, P81 and P82, foci of active microglia cells containing bright red fat were observed in the oil red O preparations These gitter cells were usually in the most central part of the demyein the center of the focus were devoid of processes, and their cell bodies were stippled with coarse granulations (fig 32) As inspection proceeded from the center of the focus, it was seen that the astrocytes gradually retained their processes, which even farther out resumed their vascular attachments and lost their stippled appearance Definite signs of hyperplasia were encountered dividing nuclei, dividing astrocytes

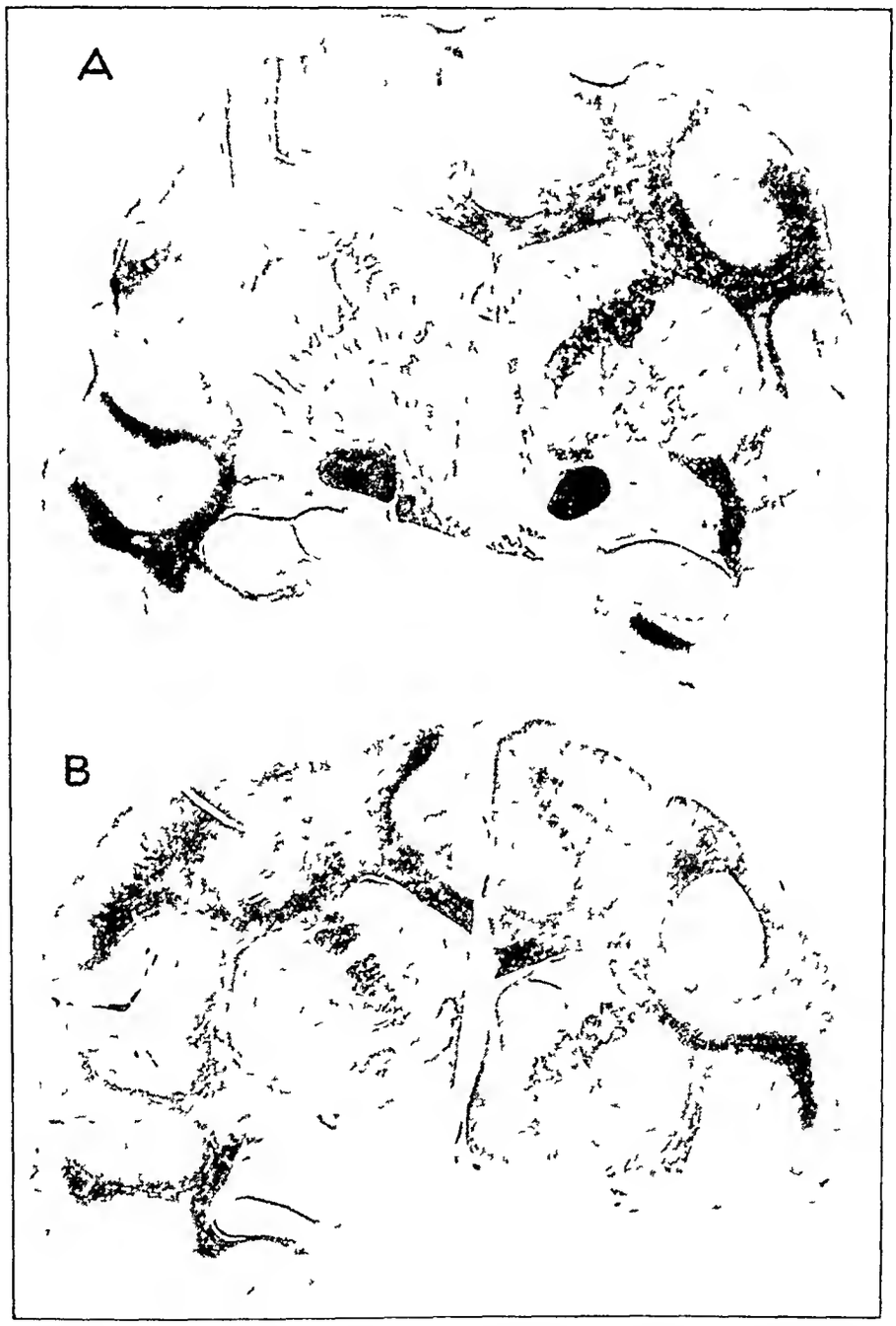

Fig 23—*A*, monkey P81 and *B*, monkey P78 Progressively extensive demyelination Block of brain of monkey P78 was split for other stains, hence the section is not quite symmetric Weil stain, × 4

linated patch and occupied, depending on the age of the lesion, one tenth or less of the demyelinated zone As in some of the dogs, hematogenous cells were present in the brain of 1 of the monkeys (fig 31) The oligodendroglia cells early became swollen, and their processes were unstainable, the nucleus and cytoplasm becoming extremely granular In the Cajal gold chloride–mercury bichloride stain, the astrocytes and paired daughter cells (fig 33) With the Holzer stain definite signs of early gliosis were observed This Holzer reaction was found in all brains which had foci of fatty necrosis but it was always extremely mild

In summary, then, it may be said of these lesions of the white matter that they consisted in demyelination which was of different ages in the different animals In some animals it had

reached the stage of breakdown of myelin in which neutral fat could be found, and in others no fat had yet been formed Furthermore, in any one focus of loss of myelin there might be fat and gitter cells in one segment of the lesion and no fat but gliocytoglial hyperplasia in another portion, while in the remaining part blanched white matter might appear in Weil or Weigert preparations but the individual sheaths might still show double refraction in frozen sections It was usually observed, however, that in any one animal, the same pattern of aging obtained in all the foci observed The lesion in its various parts was approximately of the same age in the frontal, parietal and occipital lobes This feature was observed formerly by Hurst in cases of cyanide poisoning [11]

DISTRIBUTION OF LESIONS

The alterations of the nerve cells in the supragranular layers were the most common change encountered, and they were virtually always present in the frontal lobes Of the 25 dogs only 2 failed to present, at least in some gyri, the first type of lesion of the gray matter Likewise, of the 10 monkeys, only 2 escaped this

Fig 24 (monkey P81) —Patches of demyelination in relation to blood vessels Weigert stain, × 100

Fig 25 (monkey P67) —Early loss of myelin in the subcortical white matter Frozen section, Spielmeyer stain, × 4

change in the nerve cells, and 1 of them (1633 could not be expected to show it because of the nature of the exposure The parietal lobe was also fairly constantly involved, while tables 3 and 4 indicate that this lobe was affected practically as often as the frontal lobe the impression one has from studying the microscopic slides is that the lesions of the parietal lobe were distinctly less conspicuous The occipital and temporal lobes were less commonly affected The latter, especially, was spared more often than other regions of the cerebrum, in spite of reports in the literature concerning the vulnerability this part of the brain to anoxia because of the peculiarities of its vascular architecture [29]

29 Spielmeyer, W The Anatomic Substratum of the Convulsive State, Arch Neurol & Psychiat **23** 867 (May) 1930

The cerebellum presented fewer and milder changes, this region being involved in only 10 of the dogs and 5 of the monkeys As has previously been described, long rows of Purkinje cells were often missing, pyknotic or vacuolated

TABLE 3.—*Distribution of Lesions in 25 Dogs Subjected to Anoxia* *

Dog	Frontal Lobe	Parietal Lobe	Occipital Lobe	Temporal Lobe	Basal Ganglia	Cerebellum
Judith	+	+	+	+		
Duncan		+				
Pansy	−	−	+	+		+
Lillian	+	+	+	+		
White Devil	−	+	+	+		++
						−
Casper	+		+		++	+
			+			
Allegra		+	+			
	+					
Oscar						
Horace	+	+	+	+	+	+
Sadie	−		+			+
Timothy	−	+	±	±		+
			+			
Edwin	−	+				
	±					
Patricia	+	±	+			
Harry	±	+	+	−		
Hector	±	+		+	++	±
	+				+	
Sophy	±	+		+		
	−					
Wiener	+	+−	+			
Snowball	+		+			
Tuck	+	+	+			
			+			
Terry	+	+		+		
Flora	+	+	+	++	++	
Genevieve	+	+				+
Peter	±	+	+		+	+
	+	+	+			
Victor	+	+		+	+	+
		+				
Suzy						

* The upper crosses indicate lesions in the gray matter the lower crosses, lesions in the white matter

TABLE 4.—*Distribution of Lesions in Monkeys Subjected to Anoxia in a Decompression Chamber* *

Monkey	Frontal Lobe	Parietal Lobe	Occipital Lobe	Temporal Lobe	Basal Ganglia	Cerebellum
P61		?				
P64 5	5	7	±		+	
			+			
P65	+	+	+	+		
P66	+	+	+	+	+	+
			+	+		
P67	±	+	+	+	+	±
	+	++	+	+	+	+
P78	+	+	+	+	±	+
	−	++	++	+	+	+
P80	+	+	+	+		
		+				
P81	+	+	+	+	+	+
	±±	±±+	+	+±		
P82	+	+	+	+	++	
	−+	+++	+++	±		
1633	+±−	−++	+++		+±	

* The upper crosses indicate presence of lesions in the gray matter the lower crosses, the presence of lesions in the white matter

The granular cells were not involved There seemed to be no rational system in the selection of cases with involvement of the Purkinje cells for some of the animals exposed to low degrees of anoxia presented changes, while some of the animals exposed to considerably more severe conditions were normal The changes in the basal

FIG 26 (monkey P67).—Anisotropic myelin sheaths from pale demyelinated region in serial section next to that from which figure 25 was taken Oil red O stain, polarized light, × 100

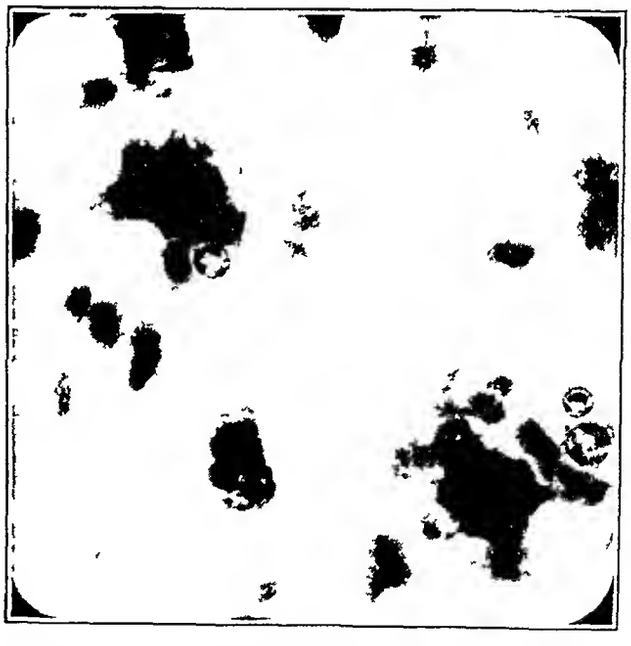

FIG 27 (monkey P80).—Disease of Betz cells Swelling and hyperchromatosis in the upper left corner and neuronophagia in the lower right corner Nissl stain, × 400

ganglia were more infrequent than those of the cerebellum (simple vacuolation and chromatolysis were not sufficient criteria of disease in cells of this region because of the nature of these cells in normal conditions)

Lesions of the gray matter of the second type were present in 8 of the dogs and in 4 of the monkeys, but not universally so, as one might infer from the literature on acute anoxia The spinal cord and medulla were the least affected parts of the central nervous system

The lesions of the white matter were distributed differently They were present in only 11 of the dogs but were found in all the monkeys but 3, 1 of which (1633) could not be expected to show them In the monkeys, in which these lesions were present with more regularity, the parietal and occipital lobes were most frequently involved, although the frontal and temporal lobes were not conspicuously unaffected There was evidently little relation between the presence of lesions of the gray matter

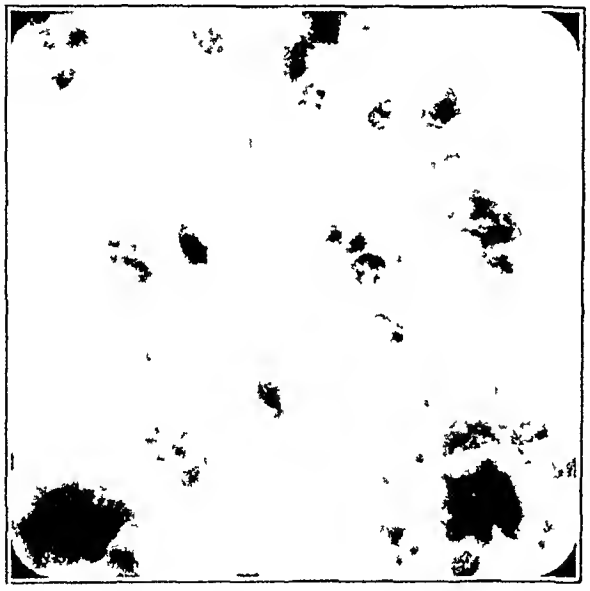

Fig 28 (monkey P67) —Betz cells with increased number of satellites Nissl stain, × 400

and that of lesions of the white matter, the universally affected gray matter of the frontal lobes, for example, was associated with involvement of the white matter in only 9 of the 35 animals

Generally speaking, the lesions were bilaterally symmetric in both the gray and the white matter The lesions of the white matter bore no special relationship to the ventricles and occurred usually in the most central portion of any white matter in which they were present The first type of lesion of the gray matter, while found almost anywhere in the supragranular layers of any affected lobe, was slightly more common, and probably more intense, over the more exposed surfaces of the gyri than it was in the depths of a buried convolution

RELATION OF OXYGEN CONTENT OF BLOOD TO DAMAGE TO THE BRAIN

Table 1 shows that the amount of oxygen in the blood of the dogs subjected to various degrees of anoxia varied from 13 to 4 5 volumes per cent, except in the case of 1 dog, which was killed during the first exposure After the desired oxygen level of the blood was reached, it was kept constant, so far as possible, during any given exposure The amount of oxygen in the blood of different dogs was kept at different levels during the exposures, but that of each particular dog was kept at the same level each day On days on which no sample of arterial blood could be obtained, because of hematoma, or for some other reason, the percentage of oxygen in the inspired air, as determined from samples taken from the collecting bag, was used instead as a measurement of the degree of anoxia to which the animal was subjected Ordinarily, there was a fairly close correlation, in the range at which these experiments were run, between the percentage of oxygen in the inspired air and the volumes per cent of oxygen in the arterial blood

As has repeatedly been stated, alterations in the ganglion cells of the supragranular layers were the first changes observed from exposures to chronic, intermittent anoxia At this point the fact is emphasized that individual differences among the animals determined to some extent their tolerance to anoxia Dog Judith, for example, received 25 exposures at an oxygen level of 13 volumes per cent and presented early lesions in all lobes of the cerebrum, while dog Duncan received 33 exposures at an oxygen level of 12 volumes per cent and had what might be called minimal lesions, and in only the parietal lobe This was the earliest alteration observed, and, while it would carry more significance if the same number of experiments could have been run on 5 or 6 animals for each oxygen level, in order to equalize, more or less, the variation due to individual differences, this oxygen level probably is not far from the threshold at which lesions begin Assuming that the hemoglobin of dog's blood is similar in combining power to that of human blood, 12 volumes per cent of oxygen in the arterial blood represents, according to Barach and associates,[30] an arterial saturation of about 78 6 per cent As the oxygen content of the blood reached lower levels, the lesions were found more consistently, provided the number of exposures was great enough But

30 Barach, A L , Brooks, R , Eckman, M , Ginsburg, E, and Johnson, A E Appraisal of Tests of Altitude Tolerance, J Aviation Med **14** 55, 1943

dog Oscar, which was subjected to anoxia with an oxygen level of 8 volumes per cent, showed no lesions of any kind, for he had been exposed only four times Dog Suzy was exposed but once to very severe oxygen deficiency She was kept for two hours close to the danger threshold (4 volumes per cent or less) and stopped breathing several times, but respiration was started again immediately, with a few breaths of fresh air, and she was then given a low oxygen mixture once more Two hours after the period of anoxia was begun she died, and the brain presented no alterations which were significant

Most of these animals presented no untoward clinical signs, and as soon as the gas mask was removed or the animal was taken from the chamber, after two or three minutes of unsteadiness, the dog was apparently recovered, with no reflex abnormalities or other objective signs But it was difficult to keep the animal alive when the oxygen level of the blood fell much below 4 or 4 5 volumes per cent Under such conditions breathing would cease, and artificial respiration would have to be used The dog might then remain unconscious for as long as twenty minutes even though he was breathing air It

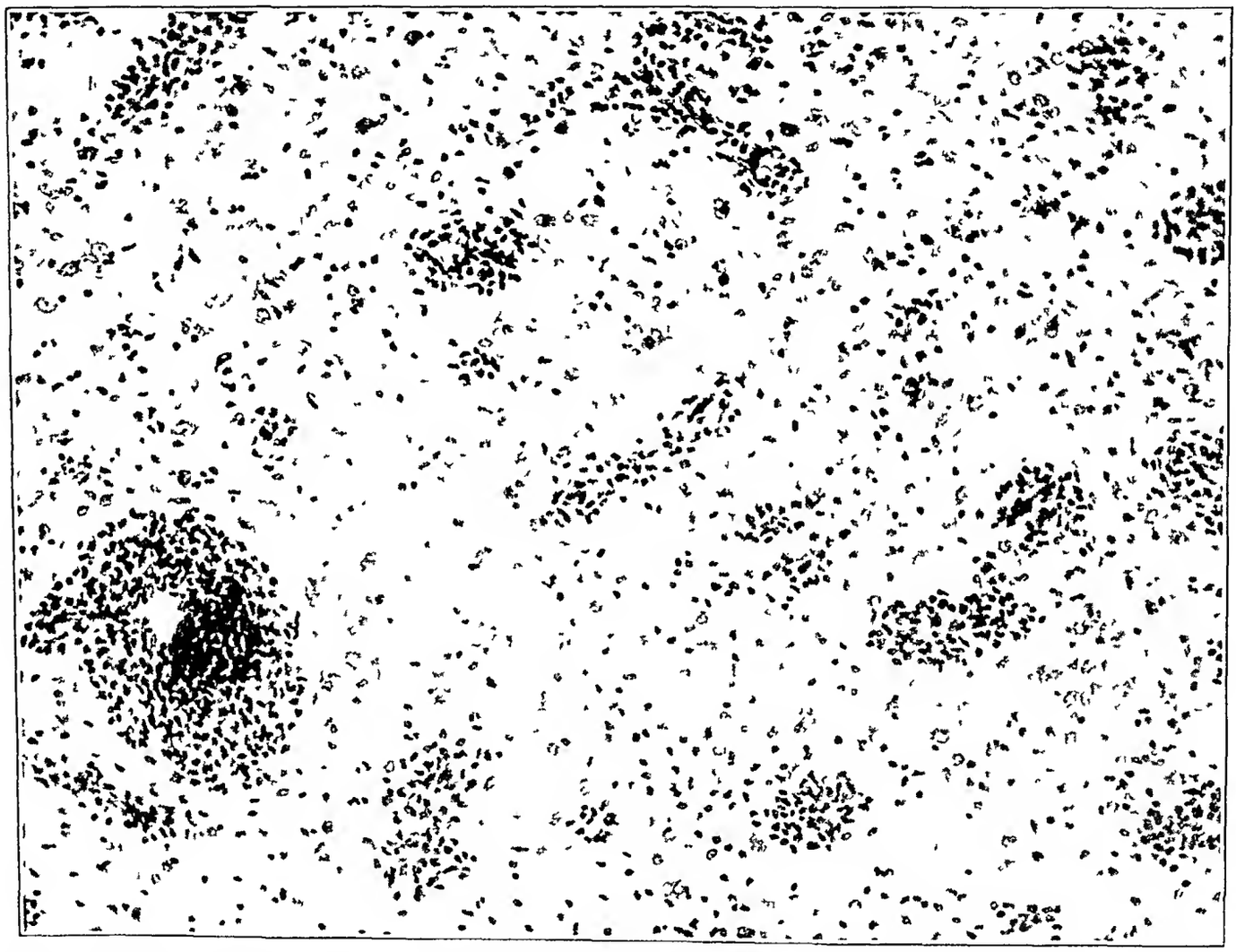

Fig 29 (monkey P82) —Dense perivascular collars of microglia cells with pleomorphic nuclei Practically none of these cells was in the gitter cell stage, although this reaction lay in the midst of a focus of demyelination Nissl stain, × 100

Here and there a few hyperchromatic cells were seen in the cortex, but no more than one can find in the brain of nearly any control dog Aside from a certain amount of hyperemia, which one usually encounters in a case of death of this nature, nothing of significance was found Evidently, two hours is too short a survival time for the production of parenchymatous alterations when the anoxia is not total This observation is interesting in view of the results reported by Weinberger and the Gibbons,[10] Tureen[9] and Gildea and Cobb[6] was in such dogs that the second type of lesion in the gray matter was apt to be found

The monkeys were exposed in a decompression chamber, and no figures were obtained on the actual oxygen content of the blood The oxygen content of the atmosphere they breathed was known, however, as well as the barometric pressure, but, presumably, the same correlation did not exist between the oxygen in the inspired air and the oxygen in the blood as was found in the dogs The monkeys were daily exposed to altitudes of 30,000 feet, where the oxygen in the

atmosphere was the equivalent of about 6 per cent at the pressure at sea level, other things being equal Such an exposure, however, is more severe than breathing 6 per cent oxygen at sea level Because of the partial pressures of water vapor and carbon dioxide in the lungs, the equivalent effect is brought down to a plane probably below the effect produced by breathing 4 per cent oxygen at a pressure of 760 mm of mercury Judging from the lesions produced in the brain, this is certainly the case, and in considering equivalent altitudes, obviously, not only the oxygen content of the blood but the tude constant and merely increasing the number of exposures resulted in lesions of both the gray and the white matter in all the remaining monkeys

REVERSIBILITY OF LESIONS

One dog (Genevieve) was kept alive three months after the last of 33 exposures to anoxia at an oxygen level of about 4 5 volumes per cent Histologic examination showed that the cerebral cortex still retained many vacuolated, chromatolytic ganglion cells in the outer cortical layers and some shrunken, pyknotic cells elsewhere

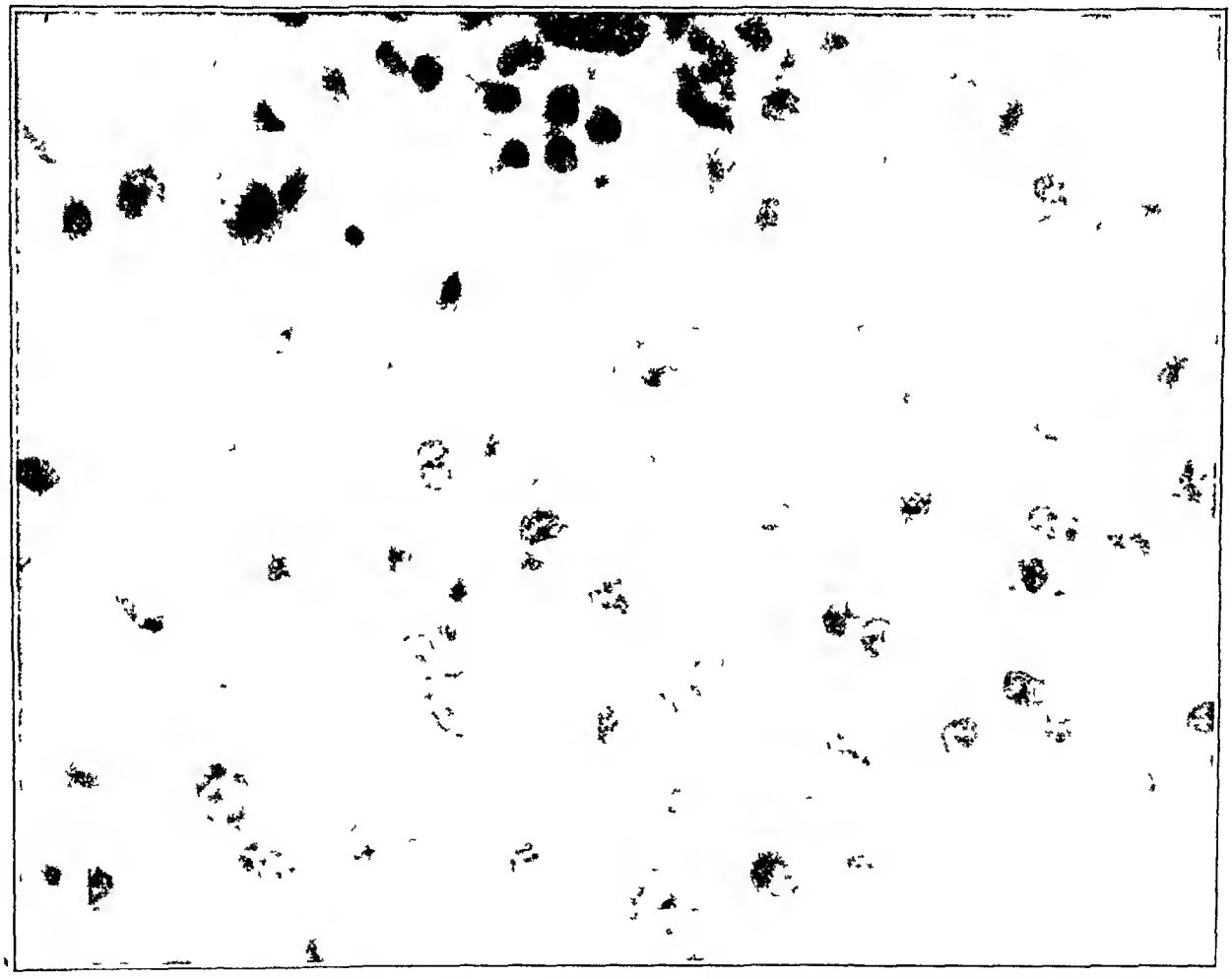

Fig 30 (monkey P82) —Plump astrocytes in the midst of the microglial reaction shown in figure 29 Nissl stain, × 400

pressure, as well as other factors with which this investigation is not directly concerned, have to be kept in mind In the series of 9 monkeys which received repeated exposures, only the first presented no alterations The second, which was treated in precisely the same way as the first, showed minimal changes in the gray matter The third, which received three times as many exposures as the first 2 monkeys, and at a slightly higher altitude, showed not only the lesions of the gray matter but the early change in the white matter of type 1 After that, keeping the altiInterestingly, however, a second dog (Tuck), which had a survival time of six months after having received 39 exposures to anoxia at a level of about 4 5 volumes per cent of oxygen, presented practically none of these vacuolated, swollen, chromatolytic cells Occasionally a few swollen cells were found in the outer layers, and even more rarely a few vacuoles, but they did not resemble the cells shown in figures 1 and 2 The tigroid substance was even in size, regular in distribution and plentiful in amount There was no chromatolysis beyond the occa-

sional cell one finds in a control brain Practically all cells with the "liquefaction" type of degeneration must have reverted to normal

The shrinkage type of cells also had undergone further changes There were fewer cells of this type than in dogs with no recovery period, and possibly fewer than in dog Genevieve (the latter comparison has little significance because of individual differences among animals), yet those still present had undergone further change Some of them were so shrunken as to be scarcely distinguishable from large microglial rod cells The shrunken, twisted cell body was of the same caliber throughout most of its length It often lay out of line of the usual cellular architechtonics, showing that its connections were probably interrupted Other shrunken cells, not so severely diseased, seen especially in the fifth layer, where the larger cells lay, presented streaked Nissl substance and increased numbers of satellites, often in rings In other words, some of the shrunken cells had reverted to normal, some had gone on to further degeneration, and some were still in the process of reaction, tending probably toward recovery after the lapse of six months With regard to the cellular reaction in the lesions in the white matter after six months' survival time, the Holzer stain showed no conspicuous overgrowth of glial fibrils, but distinct hyperplasia of the bodies of astrocytes, with paired daughter cells in abundance, was a feature The microglial reaction had partially cleared up, for the number of pleomorphic cells was extensive and the number of gitter cells still visible was small There was no dense microglial cuffing around blood vessels, but the blood vessels themselves had thickened walls not only in the center of lesions of the white matter but, to some extent, in other parts of the brain

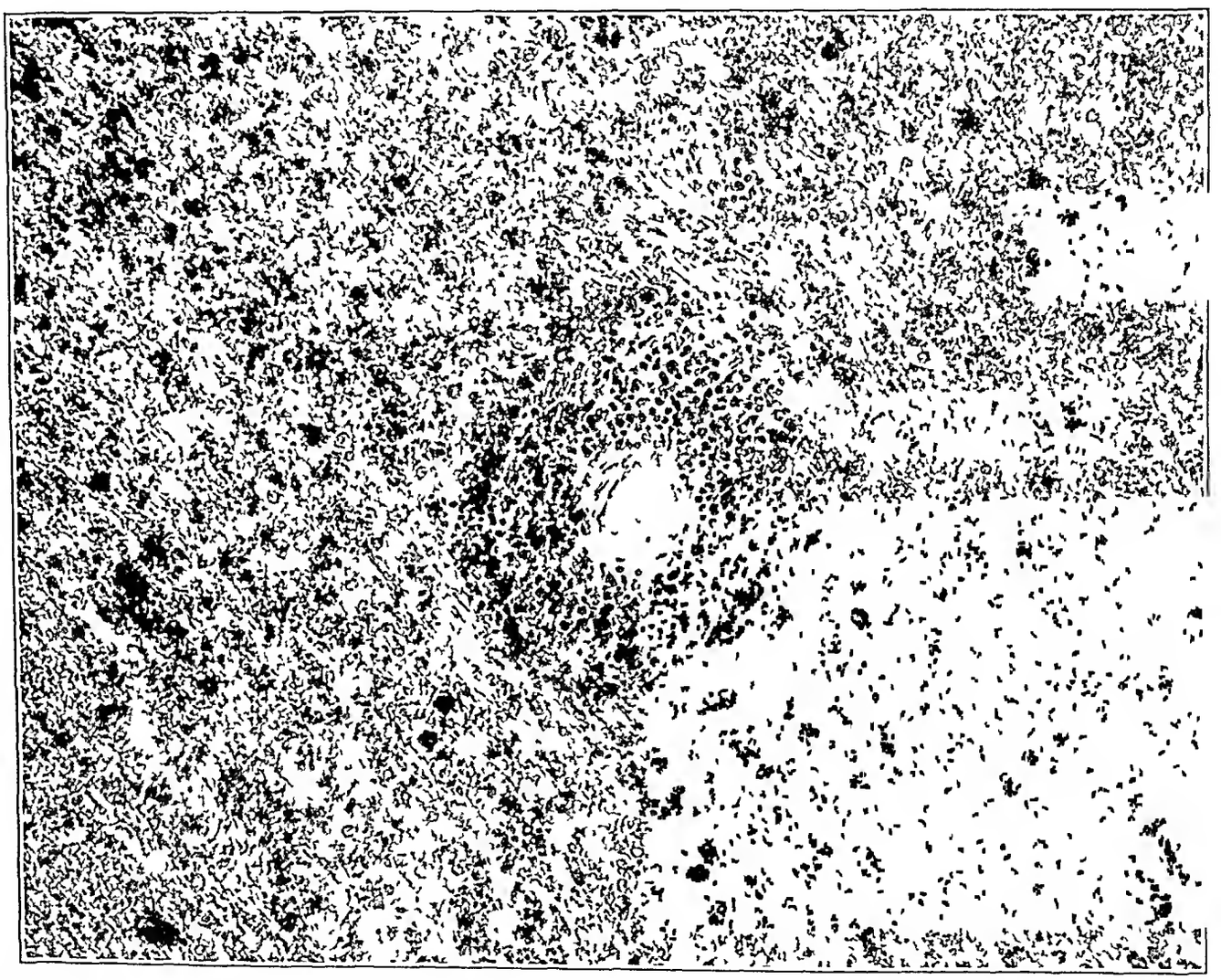

Fig 31 (monkey P66) —Perivascular cuffing with lymphocytes (and some gitter cells), while beyond the Virchow-Robin space virtually the entire field is composed of fat-laden gitter cells Oil red O stain, × 100

GANGLIA OF AUTONOMIC NERVOUS SYSTEM AND ADRENAL GLANDS

Years ago Cannon [31] expressed the view that the sympatheticoadrenal system was involved in the adaptation of the animal to anoxic condi-

31 Cannon, W B Endocrinology and Metabolism, New York, D Appleton and Company, 1924, vol 2, p 174

tions Many observations by other workers [32] since that time have confirmed this relationship It has more recently been reported by Armstrong and Heim [15] that there is hypertrophy of the adrenal glands in conditions of chronic anoxia, and this assertion was later confirmed by Thorn and his co-workers [33] Ever since the days of Claude Bernard [34] it has been known that anoxia causes glycosuria, and more recently Lewis and associates [33a] have related the increase in sugar in the blood and urine associated with acute anoxia to increased activity of the adrenal cortex the belief expressed by Armstrong and Heim [15] that the adrenal cortex was exhausted in cases of chronic anoxia

In the present investigation, the adrenal glands were studied histologically, after staining with the phenylhydrazine [22] and oil red O methods, in order to gain, if possible, an idea of the cortical activity The dogs all weighed between 10 and 12 Kg The data on the gains in weight of the adrenal glands were not significant, however, because some of the dogs were old and some were young, some were male and some were

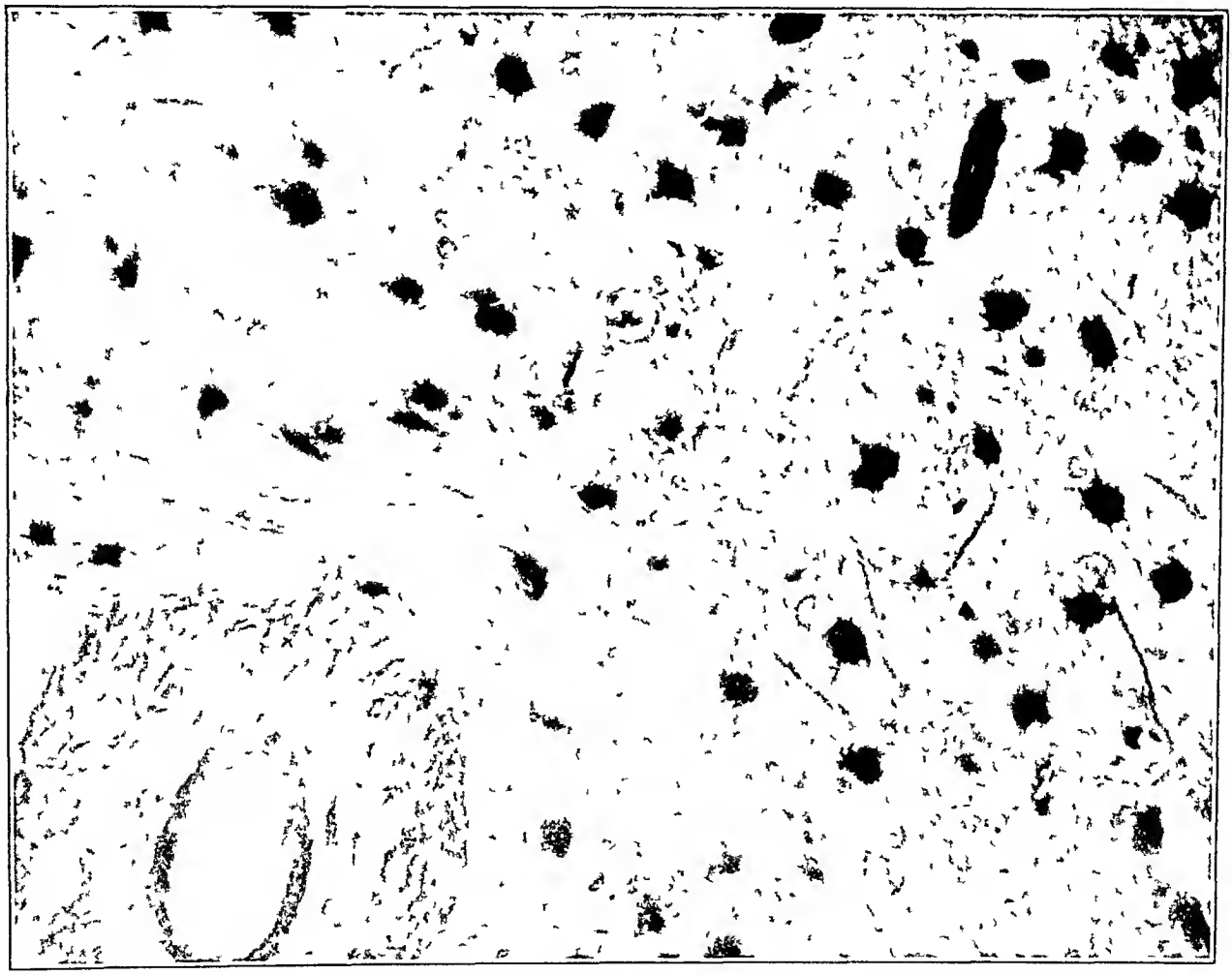

Fig 32 (monkey P66) —Field in the midst of a focus of demyelination Astrocytes have lost their processes, oligodendroglia cells are swollen, and the wall of the vessel has hyperplasia of the reticulin Cajal stain, × 100

They found, however, that in cases of chronic anoxia hypoglycemia rather than hyperglycemia was present This observation was in line with female and some lost weight during the experiment while others gained weight The weights of the adrenal glands varied from 0 41 to 1 14 Gm , and no consistent correlation could be found between the larger glands and the severity of the exposures to anoxia However, if one may

32 Evans, G The Effect of Low Atmospheric Pressure on the Glycogen Content of the Rat, Am J Physiol **110** 273, 1934, The Adrenal Cortex and Endogenous Carbohydrate Formation, ibid **114** 297, 1936

33 (*a*) Lewis, R A , Thorn, G W , Koepf, G F , and Dorrance, S S The Role of the Adrenal Cortex in Acute Anoxia, J Clin Investigation **21** 33, 1942 (*b*) Thorn, G W , Jones, B F , Lewis, R A , Mitchell, E R , and Koepf, G F The Role of the Adrenal Cortex in Anoxia The Effect of Repeated Daily Exposures to Reduced Oxygen Pressure, Am J Physiol **137** 606, 1942

34 Bernard, C Leçons sur les effects des substances toxiques et medicamenteuses, Paris, J -B Bailliere et fils, 1857

judge from the sections stained with the phenylhydrazine method, there was a degree of activity in the adrenal cortex of the animals with anoxia not present in the normal control Figure 34 shows a section of cortex of a typical adrenal gland of a dog which had been subjected to chronic anoxia, together with a neighboring section from the same gland after it had been treated with acetone to dissolve the cortical steroids Figure 35 shows similar sections from a normal dog It can be seen that greater cortical activity was present in the gland of the anoxic animal Such activity may have led to

thetic cells or in the chromaffin cells of the adrenal medulla, as seen with the cell stain, and no evidence of medullary hypertrophy was at hand

COMMENT

In the present investigation, even though only one type of oxypenia was produced, practically all the different kinds of lesions were encountered which have been reported by other authors to occur with the various types of anoxia, whether anoxic, anemic, stagnant or histotoxic The factors which varied, however, were those of time and intensity Whether the anoxia was

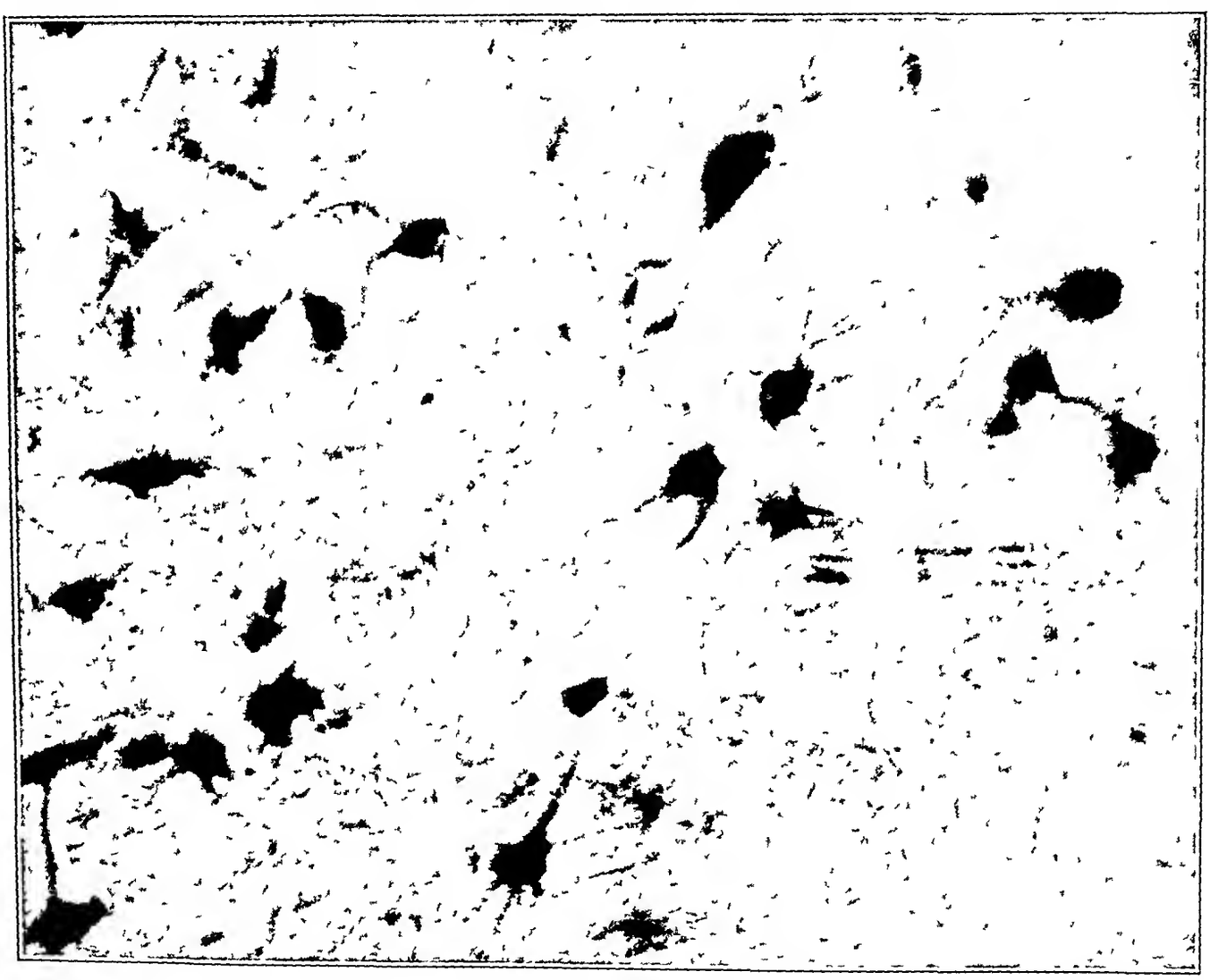

Fig 33 (monkey P66) —Feeble attempt at astrocytic hyperplasia at edge of the focus seen in figure 32 Cajal stain, × 100

early exhaustion, and in the hematoxylin and eosin preparation foam cells were often present in the fascicular layer

The nerve cells of the splanchnic ganglia often showed vacuogranular degeneration but even more frequently presented central chromatolysis with peripheral pyknosis and sometimes complete, or practically complete, lysis of the Nissl substance In some instances neuronophagia was present, together with increase in capsule cells No excessive pigmentation was observed No similar changes were present in the sympa-

acute, subacute or chronic and whether it was mild or severe made considerable difference In monkey 1633, which was exposed only once but was rather suddenly rushed to a simulated altitude of about 32,000 feet, where it remained for over twenty minutes, and then was permitted to survive for nine days, the damage to the brain was chiefly of the nature of massive laminar cortical necrosis From the histologic examination it would be impossible to distinguish the lesions in the brain of this monkey from those reported by Courville [5] or by Stewart [27] in cases

of accidental death following nitrous oxide anesthesia In both instances the anoxia was acute, overwhelming and of short duration, artificial respiration was required before normal breathing recurred and the anoxia was followed by a period of survival sufficiently long to permit the classic reactions to take place There was, obviously a hyperplasia of blood vessels with thickening of the vascular walls in the brain of this animal Courville spoke of an "astrovascular scar" in his cases, but in the case of the monkey the survival time was too short for gliosis to occur The thick vascular walls, however, presented an interesting reaction All, or nearly all, the vessels, in addition to a mild fibroblastic or collagenous thickening, had a fairly dense adventitia of reticulin as seen in Perdrau's stain (fig 20) In the Nissl preparations this reticulin could also be seen, but of course not identified, and with it rows or clusters of oligodendroglia cells This animal was not the only one in which excessive oligodendroglia cells were found in association with perivascular reticulin, especially among the dogs Dog Peter (fig 17) was another such case While it is true that dogs are more likely to exhibit perivascular oligodendroglia cells than other animals, there seemed to be a relation between reticulin and the oligodendroglia in these animals subjected to anoxia that was closer than one normally finds Years ago, Penfield,[35] in other circumstances, suggested the possibility of metaplasia of oligodendroglia into rudimentary astrocytes The "astrovascular scar" in Courville's cases and the hyperplasia of reticulin and oligodendroglia in my animals suggest the interesting thought that there may be a direct relation in the brain between formation of reticulin and the oligodendroglia

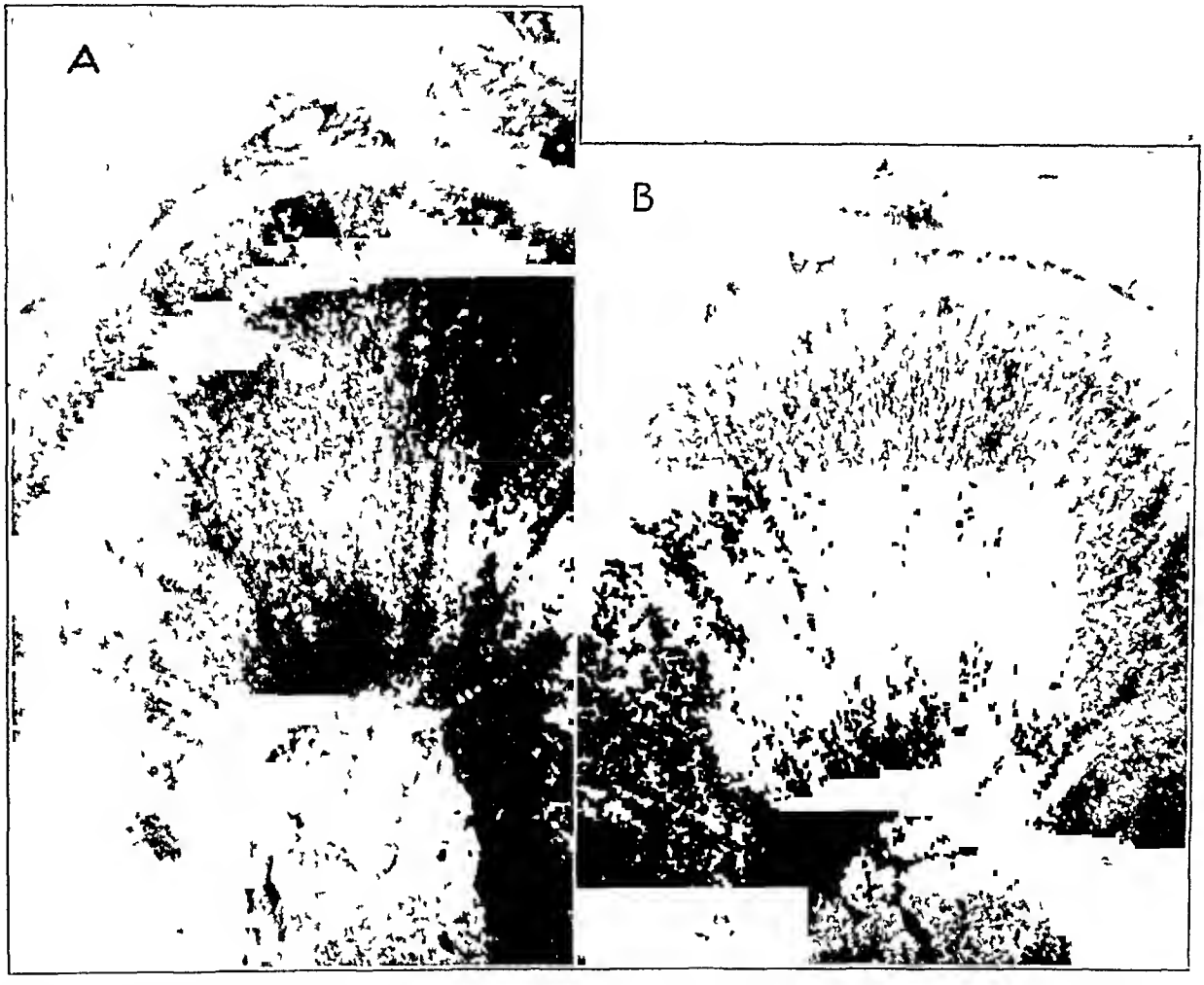

Fig 34 (dog Timothy) —Adrenal glands stained to show possible cortical activity after daily exposure to anoxia *A*, test, *B*, control Phenylhydrazine stain

In this monkey (1633) there was also a focus of softening in the globus pallidus Foci of necrosis occurred also in 3 other monkeys and in 6 or 7 dogs The clinical histories of these animals was usually slightly different from those of the other dogs and monkeys in the experi-

35 Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, vol 2, p 461

ment in that they sometimes exhibited signs of an unusual nature One monkey had a convulsion on one occasion Another had weakness of the hindlegs The dogs usually showed no untoward signs, but in several instances it could be seen, in reviewing the protocols, that "accidents" had happened during the experiment The dog would be breathing along in his usual sciousness, however, it was easy to associate, from the point of view of time, the lesion with the episode of unconsciousness The dog Casper, for example, lost consciousness during the exposure four days before death On subsequent days he showed no untoward signs Histologically, his lesions had for their distinguishing characteristic perivascular collections of hematog-

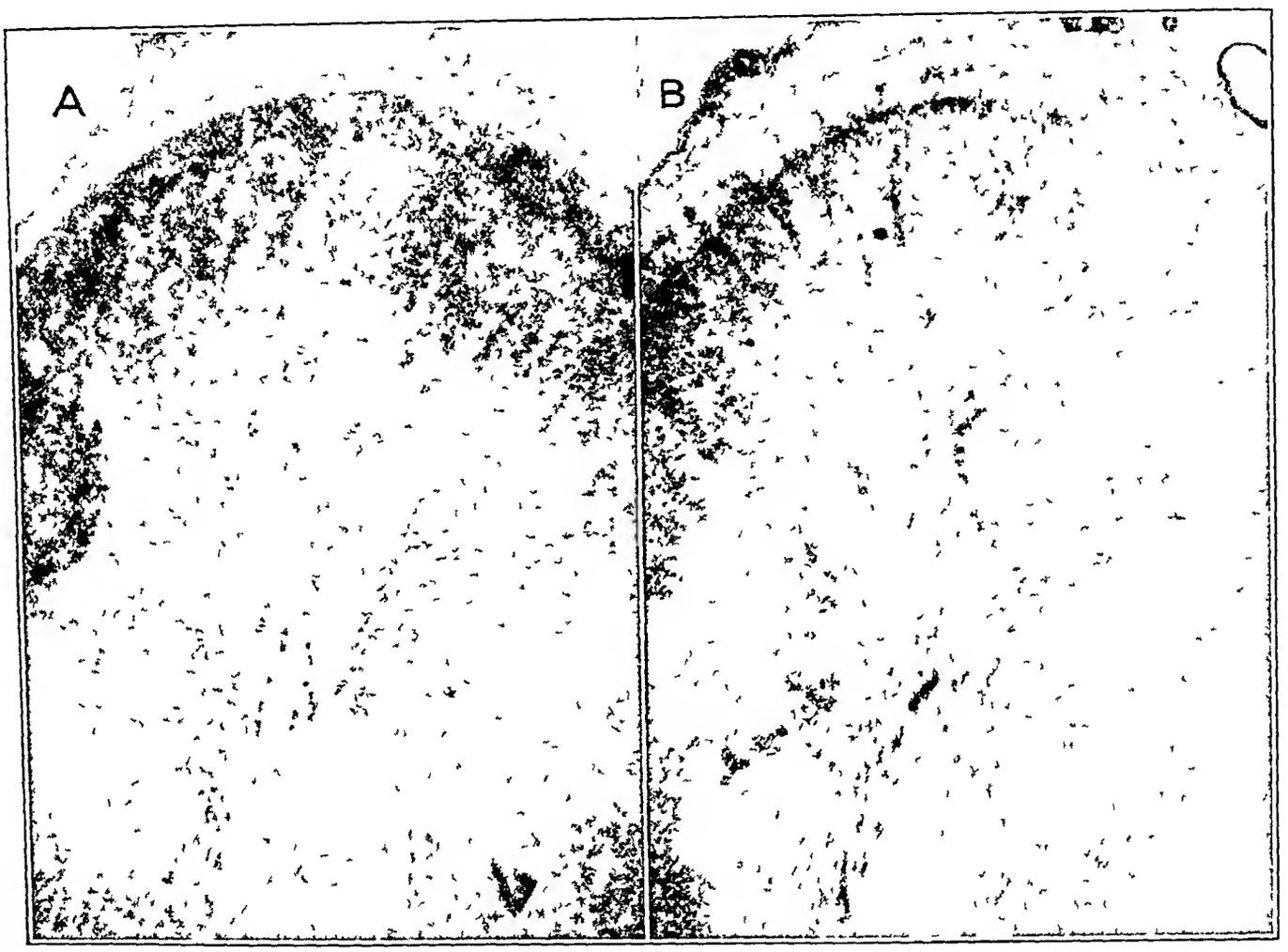

Fig 35 (control dog) —Animal not exposed to anoxia *A*, test, *B*, control Compare with figure 34 Phenylhydrazine stain

manner, inhaling the same percentage of oxygen he had formerly breathed without trouble, when suddenly he would stop breathing After a few seconds or minutes of artificial respiration he would usually breathe normally, although he might remain unconscious several minutes On one occasion such a dog remained unconscious twenty minutes On recovery, the animals appeared none the worse, and the experiment was continued For a few of the dogs, however, the protocols showed no such episodes of unconsciousness and it can only be inferred that exposures to degrees of anoxia down to the level capable of causing necrosis, either complete or incomplete, had been reached without producing clinical signs There were so many individual differences among the animals, as has been stated repeatedly, that this could very well have happened In the animals that lost con-

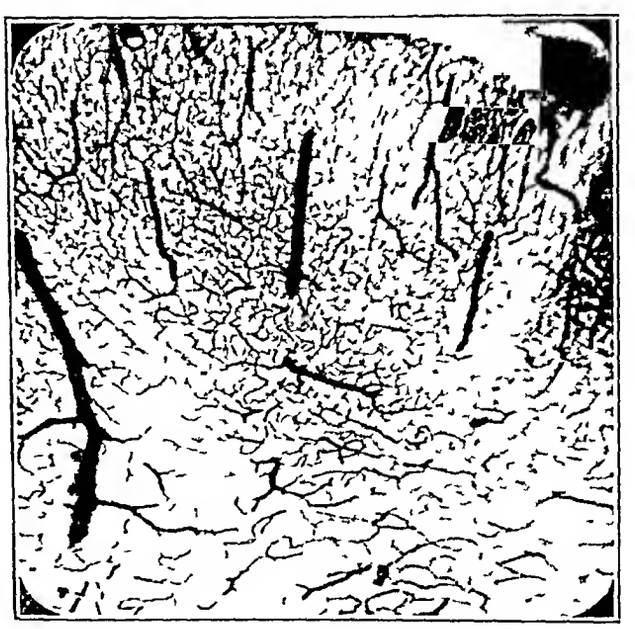

Fig 36—Vasodilatation of vessels of the fourth order Pickworth stain, × 30

enous cells, chiefly lymphocytes, the presence of which coincided perfectly with the date of loss of consciousness At the other extreme, monkey P82 had a right-sided convulsion on one occasion two months before death, and pathologically the lesion in his left occipital lobe showed, in addition to advanced necrosis, a streak of old blood pigment and, around the edge, hyperplasia of astrocytes The lesion in the dog was consistent with a four day reaction, and that in the monkey, with a two month reaction

Here, too, the method of producing the anoxia seems important In monkey 1633 the anoxia was overwhelming (for that particular animal, although another animal might have withstood it) and the induction fairly sudden, and anoxia so produced could also account for the accidents occurring during nitrous oxide anesthesia With the other monkeys and dogs of this group, however, the circumstances were rather different These animals had been subjected to anoxia before, usually many times, and on the date of loss of consciousness—if they lost it—the oxygen had been running along rather close to the danger threshold, possibly for some hours, and had only gradually slipped over into that degree of anoxia incompatible with the life of brain tissue They were immediately given pure air to breathe, so the actual duration of the dangerous level of anoxia, even though it may have been preceded by several hours of severe anoxia, was probably very brief Both these types of lesions, however, were the result of acute episodes of severe anoxia, whether or not they occurred in the midst of exposures of relatively mild anoxia of longer duration

That anoxia of a degree sufficiently intense to cause convulsions need not be long enough or complete enough to cause necrosis was shown by Gildea and Cobb [6] in their ligation experiments On the other hand, necrosis can certainly be produced by acute ligation experiments, as was recently shown by Weinberger and the Gibbons [10] By the same mechanism, thrombosis, so often found in cases of carbon monoxide poisoning,[7] could easily explain much of the necrosis associated with that type of anoxia But in the present experiment no thrombi were found, even though in several of the dogs, such as Peter and Hector, lesions were present in the thalamus which were bilaterally symmetric Whether these thalamic lesions were produced by temporary vasoconstriction (ischemic necrosis), whether the thalamus was locus minoris resistenti to low degree of oxygen saturation of the blood or whether vasodilatation to the point of stasis occurred is not known, at any rate, the thalamus was the most common site of the second type of lesion of the gray matter in the dogs

The first type of lesion of the gray matter, which was concerned chiefly with alterations in the nerve cells, was the earliest and most consistently encountered abnormality The swelling, chromatolysis and vacuolation of the cells in the supragranular layers, as well as the ischemic and chronic shrinkage in cells in the deeper layers, might be considered early physicochemical alterations, as suggested by Thorner and Lewy,[16] rather than "true degenerative changes" But such a distinction is obviously arbitrary, for severe degenerations, too, must be physicochemical The question is one of degree and of reversibility

The cytoplasm of some of the shrunken cells took a pink color with hematoxylin and eosin, and when silver preparations were made, cell bodies stood out prominently in regions where only nuclei or ghost cells could be seen with the Nissl stain Such alterations were probably often reversible, for in the 2 dogs with long survival periods such *Heide* were not seen frequently and, while there were still some cells with pronounced so-called chronic shrinkage, their number was rather small and the number of ischemic cells was insignificant

With regard to the cells of the supergranular layers, however, the problem was slightly more difficult At least 1 of the 5 control dogs presented a fairly conspicuous number of swollen, vacuolated and chromatolytic cells in the same outer cortical layers In the other control dogs, also, at least occasional cells of this type could be found, although no other pathologic change and no history or sign of disease could be obtained One great difference, however, between the animals exposed to anoxia and the controls was the difference in intensity of this type of reaction, the change being much milder even in the most conspicuously affected control The other difference was in the quality of the lesion In the exposed dogs, there was a distinct pulverization of the tigroid substance, and true vacuoles were present in the cytoplasm In the control dogs, this change was more apparent than real, for the large "vacuoles," which separated the cell membrane by a considerable distance from the rest of the cell body, gave the appearance of pseudoedematous swelling of the perikaryon The condition resembled the artefacts often produced in paraffin sections or many of those "vacuoles," for example, called "lique-

faction necrosis" in the work of Chornyak,[36] in which acetic acid was used in the fixative

Since fat was practically never present in these cells, it may be inferred that they, too, had undergone only the first stages of "physicochemical" change This was a reversible lesion, to a large extent, because, after months of recovery not many of these supragranular cells showed any traces of swelling, chromatolysis or vacuolation

One reason that these cells were not engulfed by satellites during the weeks of their abnormal condition may be that the glia also experienced these edematous changes Figure 3*B* shows swollen oligodendroglia cells among the swollen, vacuolated nerve cells, although swelling of oligodendroglia cells may be a reversible reaction, it probably precludes hyperplasia or any further adsorptive activity on the part of those cells while they remain in a swollen condition

The most common effect on the cerebral circulation of a diminished oxygen supply of the blood is vasodilatation This may go on to the point of stasis Stasis in the larger vessels of the fourth order[37] penetrating the supragranular layers on their way to the depths of the brain may well give rise to edema In fact, edema of the brain in cases of anoxia has been reported by many authors[38] The smaller caliber of the vessels (arterioles) and the less extensive capillary bed in the deeper cortical layers may account for better vasomotor tone, with the result that shrinkage rather than swelling was the response of the nerve cells observed Preparations with the methods of Pickworth and of Eros were made of some of the dog brains (fig 36), but it was early apparent that if they showed anything significant it was merely the state of the blood vessels at the time of death No conclusions could be drawn with regard to the state of the vessels during life, and if the dogs were killed by intravenous injection of pentobarbital twenty-four hours or so after their last exposure to anoxia, as they were, for other reasons, little could be inferred regarding the state of the blood vessels during anoxia It is felt that far too much emphasis is placed on this technic by certain authors[37]

Another point must be considered in discussing the alterations in the supragranular layers, namely, fatigue of the nerve cell The sequence of changes produced in nerve cells by fatigue has been worked out by Dolley,[39] Mann[40] and others[41] That nerve cells are stimulated to increased activity by anoxia is common knowledge[42] In the present experiment, in which nerve cells were exposed for four hours daily to severe oxygen want, the cells in the association layers presented the picture of almost complete exhaustion—swelling of the cell body and of the nucleus and virtual absence of Nissl substance In the deeper layers, where the process was less severe, degrees of this exhaustion picture could be found smaller cells, darkly staining Nissl substance about the periphery, especially in the ischemic cells, chromatolysis throughout the rest of the cytoplasm, a dark ring of chromatin about the nucleus, often dark nucleoplasm, and a gearlike irregularity of the nucleolus These may all be different stages of fatigue, according to the aforementioned authors, and they were found in abundance throughout the brain in this study, not only in the cortex but in the basal ganglia Unfortunately, the amount of oxygen in the arterial blood tells little regarding cellular anoxia,[43] and while there may not have been enough anoxia over such a widespread area to cause the reaction of infarction that was discussed in connection with the production of the second type of lesion in the gray matter, there may have been sufficient lack of oxygen to cause all degrees of nerve cell exhaustion Then, the fact that this anoxia was repeated, day after day, may have had an effect just noxious enough to keep the nerve cells from recuperating The combination of fatigue and anoxia, if indeed they are not the same thing, with reference to these nerve cells, may

36 Chornyak, J The Structural Changes Produced in the Human Brain by Oxygen Deprivation (Anoxemia) and Their Pathogenesis, Ann Arbor, Mich, Edwards Brothers, Inc, 1938, p 77

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42 Landis, E M Micro-Injection Studies of Capillary Permeability, Am J Physiol **83** 528, 1928

43 Hartman, F W Some Etiological Factors and Lesions in Anoxia, Am J Clin Path **8**.629, 1938

have brought about these changes independently of vasomotor conditions Regardless of the precise physiologic mechanism by which these cell changes were produced, they were the result of anoxia that was chronic, intermittent and not sufficiently severe to produce infarction in the cortical regions One believes the repetitive effect of this type of anoxia is important in producing lesions that a single exposure or a few exposures would not produce

A further accentuation of the effect of this chronic, intermittent oxypenia was seen in the lesions of the white matter While the nerve cell bodies were affected by relatively low degrees of anoxia, or by exposure to somewhat lesser degrees of anoxia repeated a greater number of times, the white matter was not, as a general thing, involved until the anoxia was even greater or the number of exposures was even higher This lesion of the white matter was an almost unique response and, so far as can be ascertained, has not been reported by any of the many previous workers on anoxia except Ferraro [13] and, later, Hurst,[14] who found it while working on experimental demyelination produced by potassium cyanide It is probable that the reaction they produced in the white matter was brought about by histotoxic anoxia acting as Hurst suggested, by the interruption of one, or several, of the enzyme system reactions within the brain At any rate, as far as experiments to produce demyelination are concerned, those in which potassium cyanide or sodium azide and the like were used are the only ones that gave consistent results As far as anoxia is concerned, in its relation to demyelination, the technic used in the present investigation, also, gave consistent results The chief factor which these two types of experiments had in common was the repetition of daily, sublethal doses over a sufficiently long time Evidently, the constant repetition is essential in the production of these lesions Since the action of cyanide is evanescent—it does not accumulate in the body—and the action of simple anoxic anoxia is likewise transient in its effects, a few breaths of fresh air relieving the anoxia, the disease of the myelin must have been the result, not of the cumulative effect of either the drug or the anoxia, but, rather, of the ultimate irreversibility of physiologic reactions that were in the intervening, recuperative hours of the early days of the experiments very largely reversible Rather than to consider the loss of myelin a specific action of anoxia on the white matter, it seems more reasonable to assume, with Hurst, that demyelination is a "type of response" to a series of episodes of anoxia no one of which would have, in itself, been capable of producing changes that were irreversible It is true that Hurst had 1 monkey which showed demyelination after thirty hours, and there was 1 dog in the present study that presented early loss of myelin in eleven days, after exposure to fairly mild anoxia, but it is emphasized again that all animals do not react in the same way However, in general, it may be said that it takes a fairly long series of exposures to a degree of anoxia which in a single exposure would be incapable of causing destruction to produce these lesions of the white matter The fact that cyanide is a potent enzyme inhibitor, in all probability, explains the demyelination produced by its daily use by Ferraro and by Hurst The production of similar lesions in the present investigation by the method of daily exposures to anoxic anoxia does not necessarily imply a similar interruption of enzyme system reactions, although it does not preclude it The same final effect may result from want of oxygen produced in either way Yet even in the present study, the chronic, intermittent nature of the exposures, coupled with the fact that the cerebral metabolism was presumably swinging back and forth between the aerobic and the anaerobic type, may well after a while have interrupted the normal enzyme system reactions

The nature of the medullary lesions seen here was not quite the same as that of the lesions reported by Hurst This may have been due to difference in technic in producing them or to difference in severity of the anoxia, or even to difference in survival time after they were produced The chief distinction was that in no instance was a peripheral reaction of histologic elements found in this investigation Hurst was able to "date" his lesions by the glial response at the periphery In the present study when there was a glial reaction it was in the more central portions of the lesion, usually, or at least often, around a blood vessel or a series of blood vessels In the earliest type of lesion of the white matter no glial response was present, there being merely a blanching of the white matter in the myelin preparations This alteration of the myelin was followed by hyperplasia of pleomorphic microglia cells in the depths of the lesion The microglia cells became normal in number and shape as the edge of the lesion was reached This was in line with the observation of Bodian and Howe,[44] in

44 Bodian, D, and Howe, H A Neural Mechanisms in Poliomyelitis, New York, Commonwealth Fund, 1942, p 233

other circumstances, in which they presented the idea that microglia cells do not proliferate in the presence of virus (poliomyelitis) but, rather, that they become hyperplastic only after the nerve cells have been damaged, that is, the hyperplasia of microglia in virus diseases is a response to injured nerve tissue rather than a response to virus The same situation obtains in the present experiment, the microglia responded to the injured myelin rather than to anoxia or to some other influence In other words, demyelination was seen first, the microglial response followed There were 1 or 2 cases in which a single slight cluster of perivascular microglia cells was present with no obvious demyelination, but it was felt that since it was not quite typical of the other microglial reactions it ought to be overlooked Besides, the demyelination, which in the early stages was not always easy to bring out, may have been missed, through a technical fault

As stated in the body of the paper, the more central parts of these demyelinated patches sometimes showed fatty necrosis, i e, the lesion was older in the center than it was on the edge The microglia had become fat-laden gitter cells, and the anisotropic myelin had lost its double refractility, had taken the stains for fat and presented the conventional myelin figures Much of this fat was scattered throughout the focus, but some of it was accumulated, in the conventional places, in the Virchow-Robin spaces and in the fibroblasts of the walls of blood vessels, whence it probably went into solution in excess of fatty acid, as Leary[45] showed in the case of cholesterol, and thence into the blood stream Not only did the gitter cells pick up neutral fat in their well known phagocytosing, but in some instances they extended their Abbau activity to anisotropic myelin

There was not much reaction to the Holzer stain in the brains of any of the animals, as if gliosis were to take an inordinately long time if, indeed, it were going to occur at all With the Cajal and Nissl stains some evidence of astrocytic hyperplasia was to be seen, as previously stated, but caution must be exercised in attributing any degree of age to the presence of plump astrocytes It is true these cells are usually seen in a chronic process, but they certainly also occur acutely, since they were present in abundance in monkey 1633, which had but a nine day survival time Some of the monkeys with severe demyelination died at altitude or were killed fairly early, after 40 or 50 exposures to anoxia, while others that were exposed to the same degree of anoxia for twice that length of time presumably had lesions as soon as the former Yet the amount of gliosis was not much greater in the latter group

It is interesting to point out that this is not the only type of anoxia with which frank gliosis failed to occur In monkeys that were exposed to chronic, intermittent insulin shocks, Finley and Brenner[46] were able to find signs of astrocytic hyperplasia but no distinct glial scars Weil and associates[47] and Tannenberg[48] obtained similar results

Regardless of whether or not the metabolism of glucose in the brain is dependent on the action of insulin,[49] insulin shock rids the brain of glucose and consequently halts metabolism During anoxia, in an effort to compensate for the lack of oxygen, the organism attempts to produce more glucose, hence the hyperglycemia associated with acute anoxia[50] Thorn and associates[33b] showed that this extra sugar comes from protein through increased activity of the adrenal cortex, there was increased adrenal cortical activity in the present experiment (fig 34) Whether anaerobic glycolysis accounts for the absence of increased glycogen in the brain associated with anoxia is not known,[51] but there was no increase in these animals This fits in well with the rest of the observations If the animals had had plenty of glucose in the brain, as there presumably is with various forms of acute anoxia, it might not have been possible to

45 Leary, T Cholesterol Lysis in Atheroma, Arch Path **37** 16 (Jan) 1944

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47 Weil, A, Liebert, E, and Heilbrunn, G Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch Neurol & Psychiat **39**·467 (March) 1938

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51 Holmes, B E, and Holmes, E G Contributions to Study of Brain Metabolism, Biochem J **19** 351, 1925, Carbohydrate Metabolism Preliminary Paper, ibid **19** 492, 1925, Carbohydrate Metabolism, ibid **19**: 836, 1925, Study of Brain Metabolism Carbohydrate Metabolism of Brain Tissue of Depancreatised Cats, ibid **21** 412, 1927 Holmes, E G, and Holmes, B E A Note on the Reducing Substances Found in Alcoholic Extracts of Brain, ibid **20** 595, 1926 Holmes, B E, and Holmes, E G Study of Brain Metabolism Carbohydrate Metabolism, Relationship of Glycogen and Lactic Acid, ibid **20** 1196, 1926

produce this new type of lesion in the white matter The oxidation systems in the brain were probably interfered with irreparably by the absence of both glucose and oxygen

SUMMARY

Twenty-five dogs were exposed daily to atmospheres of low oxygen concentration at the pressure of sea level and 10 monkeys were similarly exposed in a decompression chamber The oxygen content of the arterial blood was measured in the dogs Histologic studies were made on the central nervous systems of all the animals and on the adrenal glands of the dogs

The degree and duration of anoxia were important

It was found that a single, sudden exposure to a simulated altitude of 32,000 feet (10,000 meters) for twenty-five minutes was capable of producing extensive laminar necrosis in the cortex of the monkey

With repeated exposures to mild hypoxia, it was observed that the first histologic changes occurred in the cell bodies of the cortical gray matter This took place at a level of about 12 or 13 volumes per cent of oxygen in the blood if the exposures were long enough and were repeated often enough

When the percentage of oxygen was reduced still lower, to about 10 volumes per cent, and the number of exposures was increased, the white matter also became involved and presented a pattern of demyelination in the corpus callosum, the centrum semiovale and the adjacent fingers of subcortical white matter which, in the cases of more severe anoxia, suggested a resemblance to Schilder's disease

Aside from the lesion of the white matter, frank necrosis was usually found to occur only after episodes of anoxia sufficiently severe to produce cessation of respiration

The frontal lobe was most often involved and the temporal lobe least often The cerebellum was more frequently affected than the basal ganglia, and the spinal cord and medulla were unaffected by any degree of anoxia compatible with life An oxygen level of 4, or 4 5 volumes per cent was about as low as a dog could tolerate Respirations quickly ceased below that level

The adrenal glands showed increased cortical activity

Dr Stanley Cobb offered valuable suggestions, and Miss Margaret Carroll and Miss Ruth Harwood gave technical assistance

Massachusetts General Hospital

NEUROLOGIC MANIFESTATIONS ASSOCIATED WITH MALARIA IN DUCKS

A CLINICOPATHOLOGIC STUDY

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That persons with malaria often show symptoms suggesting involvement of the nervous system has been recognized for many years However, recently there has been an increase of interest in regard to these neurologic manifestations associated with malarial infections Harvey,[1] in 1944, reported several cases of malaria with associated neuritis Fitz-Hugh and associates,[2] in 1945, presented a large series of cases of malaria in which there was cerebral involvement McGinn and Carmody,[3] in 1944, observed that "at a base hospital, cerebral symptoms have been the most serious and frequent complication in patients suffering from malaria" Kean and Smith[4] reviewed 100 cases of estivo-autumnal malaria with autopsy and concluded that "the plugging of cerebral capillaries did not appear to be closely related to the occurrence of the symptoms of cerebral malaria" One of us (R H R),[5] in 1944, reviewed the lesions in the brain occurring with malaria and discussed their pathogenesis Dhayagude and Purandare,[6] in 1943, described the lesions of cerebral malaria, giving special attention to the malarial granulomas We[7] recently described the pathologic changes in the brain of a child infected with Plasmodium falciparum and in the brains of monkeys infected with Plasmodium knowlesi and discussed their pathogenesis We also included in our study the acute lesions occurring in the cerebellum of chicks and ducks infected with Plasmodium lophurae

The present paper considers the clinical manifestation observed in a large series of white Pekin ducks infected with malaria and describes the associated pathologic changes which were found in the nervous system of 26 of these birds[8]

CLINICAL OBSERVATIONS

The ducks used in this study were inoculated intravenously with P lophurae, and a majority of them died of the infection before the tenth day In these birds a severe anemia rapidly developed The red blood cell count frequently decreased from the normal, of 2,500,000, to 500,000, per cubic millimeter, during the acute phase of the infection The degree of parasitemia was determined by counting the number of parasitized cells per 500 red blood cells In fatal cases, 450 parasitized cells per 500 red blood cells were frequently found

The severely infected ducks became pale and weak, and within a few hours preceding death they took neither food nor water One or more convulsions usually occurred before death

Older birds given an injection of an inoculum containing fewer parasites were more likely to survive the acute infection After the crisis was passed these ducks rapidly recovered from their anemia The malarial parasites disappeared completely from the circulating blood, and then these ducks could not be distinguished from the normal controls

From the Department of Pathology, University of Arkansas School of Medicine

This study was aided by grants from the John and Mary R Markle Foundation and Eli Lilly and Company

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8 Five ducks showing neurologic manifestations were contributed to this study by Mr E R Rose, of Eli Lilly and Company

However, within a period of two to six weeks after inoculation, a majority of the ducks which had recovered from the malarial infection had neurologic manifestations A disturbance in locomotion and gait was the first change observed These ducks showed reduced volitional activity They moved slowly, lifted their feet in high steps and slapped them forcibly on the floor They maintained a broad stance, rocked to and fro and occasionally fell forward on the breast or backward on the tail When forced to move at a rapid rate, the affected ducks extended either the right or the left wing in order to prevent falling to that side

The neurologic manifestations of disturbance in equilibrium and locomotion became exaggerated when the ducks were blindfolded Furthermore, they were unable to remove the blindfold by scratching The flexed foot, instead of reaching the blindfold, was thrust away from the head with force sufficient to pivot the bird on its breast These movements of alternate flexion and extension were slowly, awkwardly and ineffectively performed

None of the ducks showed evidence of paralysis But they moved with a characteristic stiffness, and a mild degree of rigidity was present when the legs were passively moved

The ducks with the neurologic manifestations were killed at varying intervals except for a few that made a complete, spontaneous recovery The symptoms in these birds persisted for two to four weeks, during which time they gradually receded After recovery from the neurologic disturbances the ducks could not be distinguished from the controls

A majority of the birds used in this study were killed at various intervals during and after the infection by clamping the neck and immediately removing and fixing the brain Noninfected ducks were similarly killed to serve as controls A few birds were permitted to die of the disease, and their brains were removed immediately for study

PATHOLOGIC OBSERVATIONS

In the ducks which showed a high degree of parasitemia, edema, generalized vascular congestion and stasis were present throughout the brain and the spinal cord In tissues fixed either in Bouin's solution or in solution of formaldehyde U S P diluted 1 to 10 and stained with hematoxylin and eosin, the capillaries and venules were dilated, the endothelial cells were swollen and the walls of vessels were edematous The perivascular spaces were enlarged, and the surrounding nerve tissue was pale staining and reticulated Occasionally petechiae were present

In the cerebral hemispheres, the nerve cells showed early degenerative changes In hematoxylin and eosin and thionine preparations many

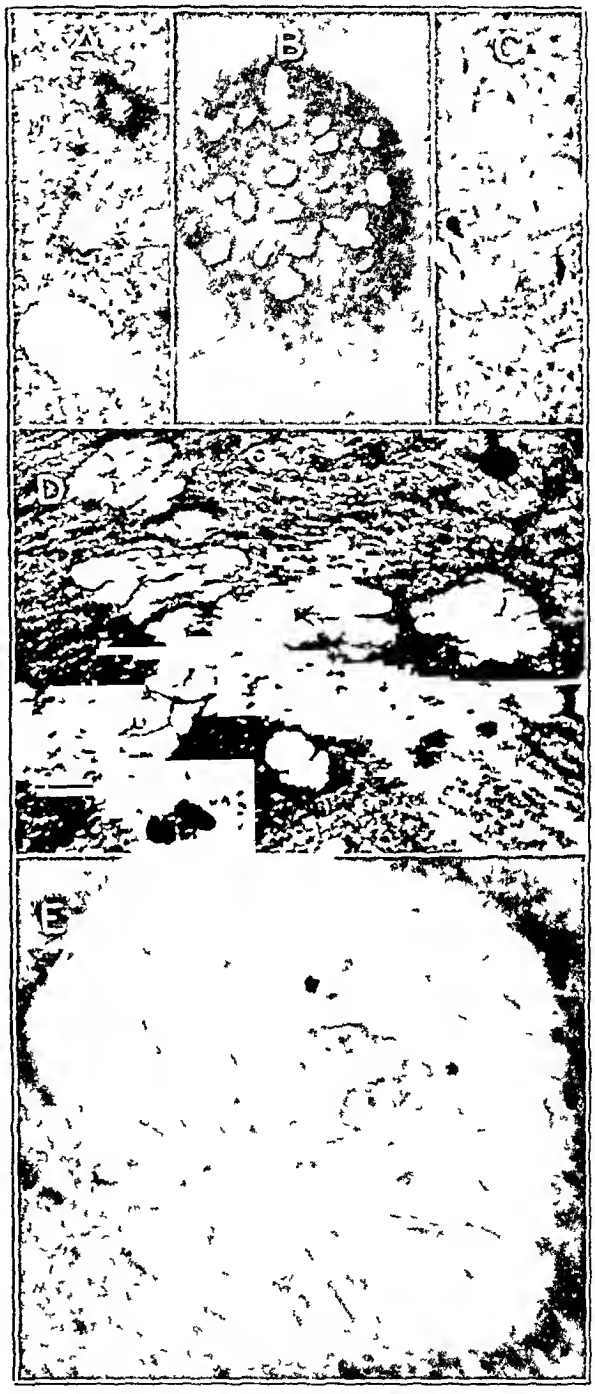

Fig 1.—Focal lesions in the brain of ducks infected with P lophurae (*A*) These lesions first appear as darkly stained areas, which gradually expand into large vesicular, fluid-filled spaces (*B*) Multiple lesions in the anterior commissure Similar lesions are present in other fiber bundles (*C*) Blood vessels are usually present within or adjacent to these focal lesions (*D*) Multiple lesions in the stratum fibrosum of the tectum A similar distribution of these lesions is seen throughout the brain stem and cerebellum (*E*) Swollen and pale-staining glial cells and nerve cells in the focal lesions The precipitated protein from the edema fluid provides a pale gray background for the photograph Hematoxylin and eosin stain

of these cells were swollen, their nuclei were vesiculated, and the chromatin material was compressed about the nucleolus The tigroid substance was centrally depleted and compressed in large masses at the periphery of the perikaryon Other cells were shrunken, their form was angular, and they stained deeply and homogeneously

In the diencephalon, the cellular changes were the same as those described in the cerebral cortex The fiber tracts, such as the forebrain bundles, the anterior and posterior commissures and the optic pathway, showed multiple focal areas of degeneration These areas varied in size They were irregularly circular, pale staining and confined to the myelinated fibers, as seen in hematoxylin and eosin preparations and in reactions stained for myelin sheaths In these lesions a few nerve fibers were demyelinated and fragmented, while the majority were crowded to the periphery and compressed Neuroglia cells, which were usually present, were swollen and pale staining, and the chromatin granules were thinly dispersed (fig 1 *E*)

The changes in the brain stem were more pronounced than those in the forebrain Many of the nerve cells here were shrunken and distorted, and their processes were corkscrew-like The cytoplasm was devoid of Nissl material and stained a muddy purple with hematoxylin and eosin The nuclei were shrunken, eccentric in position and homogeneously stained Other nerve cells showed swelling and varying degrees of chromatolysis

The brain stem was the site of numerous focal areas of degeneration, such as have been described in the diencephalon These foci were abundant along the great fiber tracts However, they were found throughout the reticular formation and in the laminations of the tectum These lesions might be so great in number as to give a cribriform appearance to sections through these regions (fig 1 *D*) Nerve cells were often involved in these areas of degeneration, and when seen they were swollen, pale staining and disintegrated (fig 1 *E*) Dilated and necrotic blood vessels were frequently noted within or adjacent to these focal lesions (fig 1 *C*) Osmic acid preparations revealed further that the nerve fibers were swollen and that the myelin sheaths were fragmented and consisted of globular masses of fat (fig 2 *A*) Bielschowsky silver preparations showed that some axis-cylinders were fragmented

Many of the Purkinje cells in the cerebellum were pyknotic and deeply stained (fig 3 *E*) Others were swollen, and the chromatin material of the nuclei was centrally compressed and separated from the nuclear membrane by a cloudy, fluid zone The Nissl substance in these cells was condensed into large flakes and displaced to the periphery of the cell body In many cells no evidence of nuclear chromatin or tigroid material could be seen Throughout the cerebellum the Purkinje cells were depleted The cells of the cerebellar nuclei showed changes

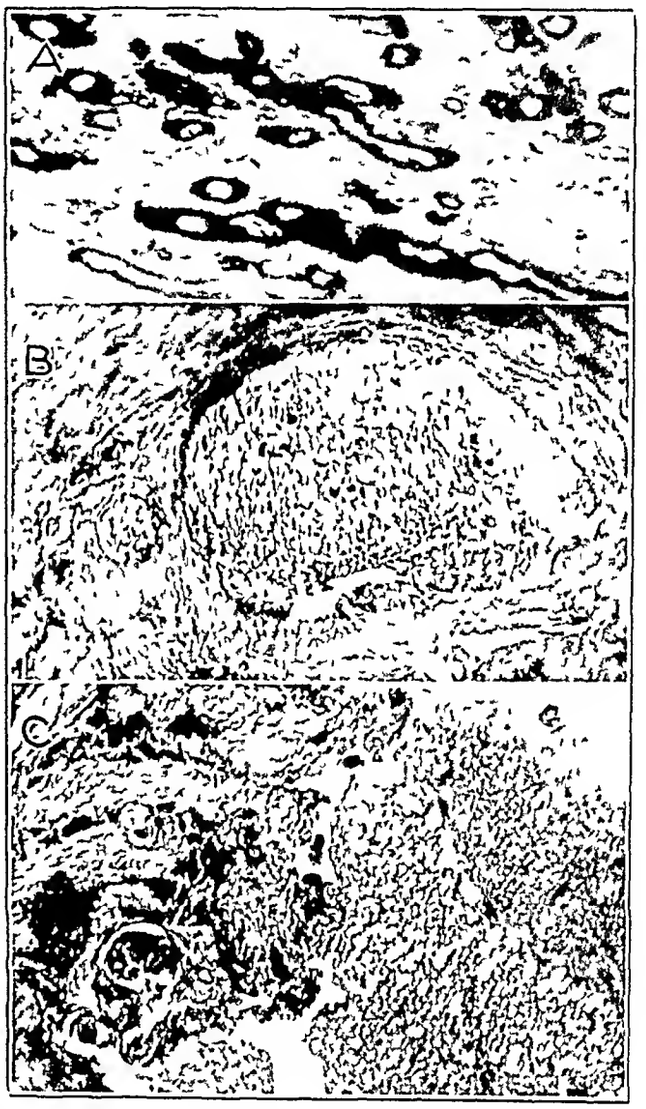

Fig 2—Extensive damage of the cranial and spinal ganglia and nerve roots (*A*) Osmic acid preparation, showing that many myelinated fibers are swollen and fragmented (*B*) Dorsal nerve root, showing extensive demyelination and fragmentation of the nerve fibers (hematoxylin and eosin stain) (*C*) Section of the trigeminal ganglion, showing destruction and depletion of the ganglion cells with fibrosis (hematoxylin and eosin stain) Round cell infiltration is present, but not visible in the photograph The adjacent nerve root shows extensive demyelination

comparable to those seen in the brain stem The granule cells, the Golgi cells and the basket cells were affected only in the moribund bird The substantia alba cerebelli contained many

focal areas of demyelination, similar to those already described (fig 1)

The changes in the spinal cord were less conspicuous The nerve cells, especially in the ventral horns, showed chromatolysis and altered staining reactions Many cells were swollen

Fig 3—Extensive injury of nerve cells throughout the brain stem and cerebellum (*A, B, C* and *D*) Swelling, vacuolation and fragmentation of nerve cells in various nuclei (*E*) Folium of the cerebellum, showing pyknosis, edema, fragmentation and depletion of the Purkinje cells This is a uniform change in all parts of the cerebellum Hematoxylin and eosin stain

The myelin sheaths and axis-cylinders in the long ascending and descending fiber pathways were swollen The ventral funiculus and the spinocerebellar tracts were more involved than other regions of the cord Rarely, a focal area of necrosis was seen in the spinal cord

Many of the cells in the cranial, spinal and sympathetic ganglia exhibited swelling and chromatolysis, and the axis-cylinders and myelin sheaths of the corresponding nerve roots were swollen

The brain and the spinal cord showed relatively few pathologic changes in the ducks that recovered from the acute malarial infection and did not present neurologic symptoms The edema, which was a conspicuous feature in the ducks during the acute illness, was no longer present The nerve cells throughout all portions of the nervous system in the ducks which did not show neurologic symptoms exhibited only minor alterations in structure and staining reactions, changes which were comparable to those seen in the normal controls except in the cerebellum, where the Purkinje cells were reduced in number

The focal areas of degeneration, so conspicuous in the brain in the acute process, were greatly reduced in size and were filled in with glial tissue They now appeared as irregular, pale-staining areas, in which the fibrous and glial matrix was less dense than the surrounding tissue

In the ducks in which clinical neurologic disturbances developed the brains and cords showed in an exaggerated form all the characteristic lesions seen in the acute infections Edema was a marked feature The nerve cells, especially in the brain stem and the cerebellum, showed advanced degenerative changes The cytoplasm, devoid of Nissl material, stained a muddy pink with hematoxylin and eosin, and the cells had a pale, shaggy appearance when stained with thionine Many cells showed vacuolar degeneration and fragmentation of the nucleus and perikaryon (fig 3) The nuclear masses functionally associated with the tectospinal, bulbospinal and spinocerebellar tracts and with the median longitudinal fasciculus were more extensively involved than the remaining nerve cells The Purkinje cells and the cells of the cerebellar nuclei showed advanced degenerative changes

The focal areas of degeneration in the birds with neurologic manifestation were larger and more numerous than they were in the birds with acute malarial infection The ascending and descending pathways connecting the brain stem and cerebellum to the spinal cord showed pronounced swelling of the nerve fibers, with considerable fragmentation of the myelin sheaths The motor pathways were more involved than the sensory tracts These degenerative changes

were conspicuous in the median longitudinal fasciculus and the tectospinal, bulbospinal and spinocerebellar tracts

The focal areas of degeneration, which were so conspicuous in the ducks showing neurologic symptoms, now appeared in these ducks which

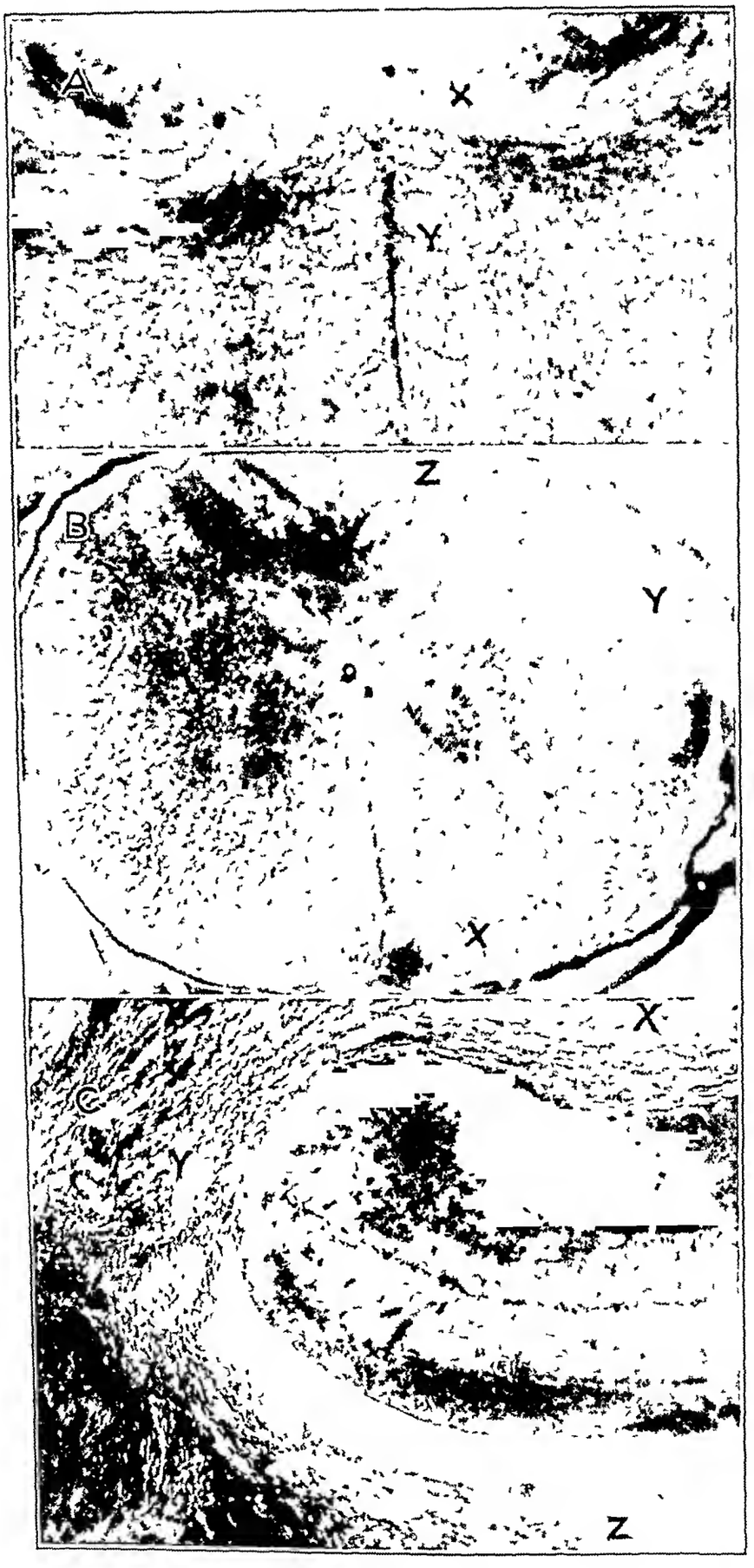

Fig 4—Extensive demyelination of the fiber tracts functionally associated with the cerebellum in ducks which have recovered from the neurologic manifestations (*A*) Section through the medulla, showing extensive demyelination of the median longitudinal fasciculus (*X*) and the tectospinal tract (*Y*) (*B*) Section of the spinal cord, showing demyelination of the ventral funiculus (*X*), the dorsal and ventral spinocerebellar tracts (*Y*) and the dorsal fasciculus proprius (*Z*) (*C*) Section showing demyelination of the cerebellar commissure (*X*), cerebellar peduncle (*Y*) and median longitudinal fasciculus (*Z*) Hematoxylin and eosin stain

had completely recovered from their neurologic disturbances as small, barely visible, pale-staining areas No significant changes were observed in the nerve cells except that there was a notable depletion of the Purkinje cells in the cerebellum and an occasional fragmented cell in various nuclei of the brain stem

In the medulla, the median longitudinal fasciculus, the tectospinal and spinocerebellar tracts (fig 4 *A*) and the cerebellar peduncles and cerebellar commissure (fig 4 *C*) had undergone extensive demyelination The spinal cord also showed marked demyelination of the ventral funiculus and moderate involvement of the lateral funiculus, especially the dorsal and ventral spinocerebellar tracts, and the fasciculus proprius of the dorsal funiculus (fig 4 *B*)

The trigeminal ganglion showed marked depletion of the ganglion cells with extensive fibrosis and infiltration with round cells and fibroblasts (fig 2 *C*) The remaining ganglion cells appeared homogeneous and deeply stained The emerging nerve roots were distorted, and their fibers were swollen and fragmented (fig 2 *B* and *C*)

COMMENT

The clinical manifestations as observed in ducks with malaria may result from the pathologic changes noted in the nervous system The lesions which occur in the nervous system during the acute phase of the infection are edema of the tissue, alterations in the staining reactions and morphologic features of the nerve cells and degeneration in the fiber tracts The last-mentioned change may appear either as swelling and fragmentation of the myelinated nerve fibers or as focal lesions closely associated with blood vessels The appearance of the focal lesions suggest that they are pockets of fluid In this respect they are similar to the perivascular necrosis frequently observed in the human brain and considered to be the result of edema However, these lesions are more numerous in the duck and, because the pressure of the accumulated fluid displaces the nerve fibers and glial elements to the periphery of the area, are more impressive than those seen in man

The changes in the nerve cells are identical with those observed in the brains of man and monkey infected with malaria,[7] in dogs and cats following experimental arrest of the cerebral circulation[9] and in the human brain following ischemia[10]

Pyknosis and hyperchromia are the first changes observed in the nerve cells during the course of the infection These are followed, in turn, by chromatolysis, edema of the cell, vacuolation of the cytoplasm and cellular disintegration The rapidity, severity and duration of the infectious process apparently determine the degree of cellular changes seen in any given case There are differences of opinion among investigators as to the sequence and significance of these various cellular changes The observation made in this study supports the interpretation of Gildea and Cobb[9b] that pyknosis represents the acute reaction of nerve cells to ischemia, while the edematous stage represents the more chronic reaction The early responses result from stimulation of the cell and are normal physiologic changes The later responses result from irreparable damage to the cell and are pathologic changes Just where the line separating the normal from the abnormal is to be drawn in this series of events is a matter of opinion

The earlier changes in both the nerve cells and the fiber tracts apparently are reversible, since they disappear with recovery from the malarial infection It is suggested that as the degree of the parasitemia decreases and the red blood cell count rises, the normal osmotic relations are gradually restored, in consequence of which the edema recedes As the fluid is withdrawn from the tissues, the nerve fibers and glial elements, released from pressure, again fill in and largely obliterate the focal lesions The nerve cells also respond favorably to the improved osmotic conditions Recovery from the clinical symptoms accompany these morphologic changes

Many of the ducks which recover from the acute infection later manifest pronounced neurologic disturbances These are accompanied with conspicuous pathologic changes in the nervous system Similar observations have been made by other investigators, in various studies, but the mechanism for these delayed clinical manifestations is not known Kabat,[11] Dennis and Kabat,[12] and Kabat, Dennis and Baker,[9a] by use of the cervical pressure cuff, completely arrested the cerebral circulation in dogs for periods of

9 (*a*) Kabat, H , Dennis, C, and Baker, A B Recovery of Function Following the Arrest of the Brain Circulation, Am J Physiol **132** 737-747, 1941 (*b*) Gildea, E F, and Cobb, S The Effects of Anemia on the Cerebral Cortex of the Cat, Arch Neurol & Psychiat **23** 876-901 (May) 1930

10 Courville, C B Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif, Pacific Press Pub Assn, 1939

11 Kabat, H The Greater Resistance of Very Young Animals to Arrest of the Brain Circulation, Am J Physiol **130** 588-599, 1940

12 Dennis, C, and Kabat, H Behavior of Dogs After Complete Temporary Arrest of the Cephalic Circulation, Proc Soc Exper Biol & Med. **40** 559-561, 1939

two to twelve minutes Several of the dogs remained in coma for twenty-four to thirty-six hours, after which they manifested ataxia, tremor and loss of spontaneous activity Courville,[10] while studying the effects of nitrous oxide anesthesia on the nervous system of man, observed that frequently an interval of several hours, days or weeks elapsed between the administration of the anesthetic and the appearance of the neurologic manifestations

The lesions which are found in the ducks with neurologic manifestations, although more extensive, are identical with those present during the acute infection If the opinion is correct that the pathologic changes occurring during the acute infection result from the altered cellular metabolism and from the accumulation of edema fluid incident to vascular disturbance, it is reasonable to believe that the subsequent lesions have a similar etiologic basis The pertinent question is what factor produces these delayed vascular disturbances The birds at the time of death did not appear to be anemic, and parasites were not demonstrated either in the peripheral blood or in stained sections of the brain Therefore one cannot attribute the secondary vascular disturbances to an exacerbation of the infectious process

It is of interest to know that Courville [10] observed remissions and exacerbations of symptoms with progressive neural deterioration in patients who had suffered cardiorespiratory failure under nitrous oxide oxygen anesthesia It was his expressed opinion that these delayed clinical and pathologic manifestations result from vasomotor instability He stated (page 69) [10]

> anoxemia so impairs the vasomotor control of the cerebral blood vessels that abnormal fluctuations in the vascular bed result, and these fluctuations are manifested clinically by remission or exacerbation in the patient's symptoms This perverted action of the vasomotor system probably continues or even accentuates the destructive process It is still another bit of evidence that asphyxia simply initiates the degenerative process, and the end results become evident only after a sufficient interval of time has elapsed

Regardless of whether or not vasomotor instability is an adequate explanation, the fact remains that this subsequent disturbance is accompanied with a considerable degree of edema, extensive demyelination of the fiber tracts, necrosis of nerve cells and clinically manifest neurologic signs These pathologic changes in the brain and spinal cord apparently are irreversible They involve primarily the nuclei and sensory and motor tracts associated with the cerebellum and its functions

The clinical manifestations shown by the ducks are definitely those resulting from cerebellar dysfunction Muscular weakness, loss of coordination and ataxia are typical manifestations of cerebellar deficiency The to and fro rocking motion and the inability alternately to flex and extend the leg and foot are analogous to the Romberg sign and adiadokokinesis observed in man Furthermore, the symptoms are exaggerated when the ducks are blindfolded, which is also the case in man with lesions in the cerebellum It is of interest that the neurologic manifestations exhibited by the experimental animals of Kabat and his associates [9a] were cerebellar in nature and that in many cases reported in the literature in which neurologic disturbances followed malaria in man cerebellar, in addition to cerebral, symptoms were shown

Although these advanced pathologic changes in the nervous system are irreversible and persist, the affected ducks after several weeks make a satisfactory clinical recovery Kabat's dogs, likewise, recovered from their neurologic disturbances It is well recognized that birds, as well as many lower mammals, readily recover from the symptoms produced by partial or complete destruction of the cerebellum In case of extensive damage to the human cerebrum and cerebellum, full clinical recovery should not be expected

The spinal and cranial ganglia and their associated nerve roots were injured in most of the ducks infected with malaria In some birds the damage was extensive This is interesting in view of the clinical observations that patients with malaria commonly complain of neuritis (Harvey [1]) Bargeton [13] found that complete suppression of the blood supply to a sympathetic ganglion resulted in complete loss of activity, which was readily restored on removing the arterial obstruction Repeated experiments on the same ganglion, however, led to rapid exhaustion, to slowed reaction and to delayed recovery of the cells

Cannon and Burket [14] observed morphologic changes in the ganglion cells of the mesenteric plexus within three hours after occlusion of the blood supply After three and a half hours practically all cells either had disappeared or were disintegrating We have frequently observed in both ducks and chicks infected with malaria a depletion and fragmentation of cells

13 Bargeton, D Some Effects of Acute Anemia on the Transmission of Impulses Through a Sympathetic Ganglia, Am J Physiol **121** 261-269, 1938

14 Cannon, W B, and Burket, I R The Endurance of Anemia by Nerve Cells in the Myenteric Plexus, Am J Physiol **32** 347-357, 1913

in the celiac and aortic chain of ganglia In view of the changes in the various ganglia and nerve roots, it is reasonable to assume that sensory disturbances were present in the ducks, although they were not evaluated in this study

In a previous paper discussing the lesions in the brain associated with malaria," we presented the concept that the pathologic changes result from anoxia We believe, also, that anoxia is the primary etiologic factor responsible for the pathologic changes in the nervous system of ducks This opinion is supported by the fact that we have experimentally produced identical lesions in ducks and chicks placed in the low pressure chamber

Clinical and experimental observations show that pronounced anemia results from the rapid destruction of red blood cells by the malarial parasites The oxygen-carrying capacity of the blood is thereby reduced This anoxemic state not only affects the brain directly but produces a generalized circulatory "failing," which further increases the cerebral anoxemia and leads to cerebrovascular stasis and ischemia of the brain tissue Increased capillary permeability results from damage to the capillary endothelium Fluid escapes from the capillary walls into the perivascular spaces and the adjacent nerve tissue Edema is thus produced This results in stasis of the tissue fluids Oxygen is thereby excluded from the tissue, and carbon dioxide accumulates in the pericellular and perivascular spaces This leads to dilatation of the blood vessels and thus to further vascular stasis The excessive accumulation of the edema fluid in the tissue spaces may produce the focal areas of degeneration which have been described The depletion of oxygen to the nerves fibers and the pressure of the surrounding fluid lead to swelling, fragmentation and degeneration of the myelin sheaths The nerve cells similarly affected undergo alterations in their size, shape and staining reactions They become edematous and eventually fragment and disintegrate The clinical manifestations are only the physiologic expressions of these morphologic alterations

SUMMARY

Ducks severely infected with P lophurae showed injury to the brain, spinal cord and peripheral ganglia and nerves Pronounced edema, focal areas of degeneration in the fiber tracts, extensive demyelination of the nerve fibers, and pyknosis, edema and fragmentation of the nerve cells are the characteristic lesions The nuclei and fiber tracts functionally associated with the cerebellum are the structures most extensively damaged These pathologic changes are accompanied with clinical manifestations of cerebellar dysfunction, such as ataxia, incoordination and disturbances of posture and equilibrium It is suggested that anoxia, which results, first, from the anemia produced by the rapid destruction of red blood cells by the parasites and, second, from vasomotor instability and circulatory failure, is the etiologic factor responsible for these pathologic changes

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NYSTAGMUS

AN APPRAISAL AND A CLASSIFICATION

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Nystagmus is a common sign in diseases of the nervous system, and it is also observed in diseases of the eye and of the inner ear It may, however, be a normal phenomenon in certain circumstances, or it may be elicited experimentally or as part of the clinical examination There are many varieties of nystagmus, and the manifestation should not be considered as an entity In order to evaluate the significance of the presence of nystagmus in any individual instance, one must understand the underlying mechanisms and the mode of production of the phenomenon

Nystagmus, or, as it is sometimes called, talantropia,[1] may be defined as an involuntary oscillation or trembling of the eyeball The term "rhythmic" is often included in the definition, but nonrhythmic varieties may be seen Certain observers object to the inclusion of the adjective "involuntary," as nystagmus of volitional origin has been described Nystagmus is a coordinated movement, and usually the two eyes move synchronously over a virtually equal range Unilateral nystagmus, however, may occur, or there may be dissociation of movements or disproportion between the movements on the two sides The motor response involves not only the contraction of certain muscles but the relaxation of their antagonists by reciprocal innervation, with alternating activity of agonists and antagonists [2]

Nystagmus may be described in various ways, namely, as to type, form, direction, rate, amplitude, duration and intensity, and as to the relation of the response to movements of the eyes, head and body It may be rhythmic or pendular in type In rhythmic, or resilient, nystagmus, also known as jerky, biphasic, directed or spring nystagmus, there are alternate slow and quick ocular excursions, resulting in jerky, unequal oscillations of the eyeballs Usually there is a rapid movement in the direction of gaze, which is followed by a slower return movement away from the point of fixation In pendular, or undulatory, nystagmus there are more or less regular to and fro movements of approximately equal range and velocity toward each side of a central point

Nystagmus may be horizontal, vertical, oblique, rotatory or mixed in form and may be directed to the right or left, or upward or downward In rotatory nystagmus the direction is recorded as clockwise or counterclockwise to the right or to the left Nystagmus may be slow, medium or rapid in rate, or velocity, and may vary from 10 to 1,000 oscillations per minute [3] It is said that if the movements are from 10 to 40 per minute the nystagmus is slow, it is medium in velocity if the oscillations are between 40 and 100 per minute, and it is rapid if they are over 100 per minute Nystagmus is classified as to amplitude, being fine, medium or coarse The movements may be so gross that they cannot be overlooked, or they may be so fine that they cannot be seen with the naked eye but are visualized only when the eye is examined with the ophthalmoscope or when a + 20 00 D lens is placed in front of the eye The use of the convex lens not only magnifies the nystagmus but eliminates fixation It is said that if the excursions are of less than 5 degrees or less than 1 mm in amplitude the nystagmus is fine, if they are over 15 degrees or more than 3 mm in amplitude the nystagmus is coarse and if they are between these values the nystagmus is considered of medium amplitude [3] From the standpoint of duration nystagmus may be abortive or sustained It may also be classified as to intensity, it is said to be of first degree intensity if present only when the subject is looking in the direction of the quick component, of second degree intensity if present not only when he is looking in the direction of the quick component but when the eyes are in the neutral position, and of third degree intensity

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1 Peter, L C The Extra-Ocular Muscles A Clinical Study of Normal and Abnormal Ocular Motility, ed 3, Philadelphia, Lea & Febiger, 1941, p 293

2 Duke-Elder, W S Text-Book of Ophthalmology, St Louis, C V Mosby Company, 1939, vol 1, p 630

3 Spiegel, E A, and Sommer, I Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc, 1944, p 104

if present even when he is looking in the direction of the slow component

Nystagmus may be congenital or acquired, it may be spontaneous or artificial (or induced), it may be present at rest, on fixation or on deviation of the eyeballs Nystagmus may be associated or conjugate, with the movements symmetric in the two eyes, or dissociated, with the movements of the two eyes unrelated In unilateral nystagmus the movements are seen on one side only In disjunctive nystagmus, which is rare, the movements are symmetrically opposite A movement that appears to be simple to the naked eye may be seen to be irregular or complex when visualized through the ophthalmoscope or through a lens Nystagmus may vary from time to time in the same person, depending on such factors as the position of the body, the head and the eyes Nystagmus may be maintained or unimpaired in the presence of extensive ocular palsies [2] Rhythmic movements of the head may accompany nystagmus Patients with nystagmus may notice a sensation of movement at the onset of the manifestation, or they may notice a constant movement of the objects within the field of vision, this subjective manifestation is known as oscillopsia and is relatively rare [4]

Various methods have been described for the delineation and recording of nystagmus Among the modes first utilized were mechanical means such as that of Ohm,[5] who placed tambours against the closed eyelid, using a pneumatic tube to transmit the movements of the eyeball to a kymograph With later methods the electrical potentials set up by ocular movements were recorded, either an oscillograph with an amplified pick-up, basically a modified string galvanometer,[6] or a vacuum tube amplifier [7] being used to show resistance capacity All these methods have certain drawbacks, however The pressure of the tambour and the lag in conduction of the impulse may inhibit or diminish the recording of the amplitude and duration of the movement With the electrical methods, the electrodes are attached to the outer canthi or to the temples, and one gets a recording not only of the movements of the eyeball but of the movements of the eyelid, the orbicularis muscle and the head In experimental work the electrodes can be attached to the anesthetized cornea or to the ocular muscles, but these methods are not applicable to clinical study

Photographic methods have been used by Dodge and Fox,[8] Linthicum [9] and others The first-named authors pressed a concave mirror against the closed lid of one eye tangential to the underlying corneal surface, and this reflected a recording beam of light on moving photographic paper, thus showing the conjugate movement of one eye as the other moved in response to visual or other stimuli With this method, also, movement of the levator and orbicularis muscles, tremors, movements of the head and fatigue influence the recording Linthicum focused a beam of light against the eye, and the corneal light reflex was focused on a continuous photographic film Cinematography has also been used, but it is difficult to record the amplitude and rate with this method At present there is no clinically applicable method with which nystagmus is adequately recorded so as definitely to delineate rate, amplitude, type, duration and intensity The character and extent of the oscillations may be most satisfactorily studied by means of the slit lamp, utilizing the f/55 objective with a micrometer ocular, this enables the observer to study the character of the movement and to measure the amplitude of the oscillations The Ferree-Rand perimeter can also be used for similar observations [10]

Nystagmus must not be regarded as an entity, for there are many types of nystagmus which appear to serve widely diverse purposes The position of the eyes is influenced reflexly by

4 Brickner, R M Oscillopsia A New Symptom Commonly Occurring in Multiple Sclerosis, Arch Neurol & Psychiat **36** 586 (Sept) 1936

5 Ohm, J Ein neuer Nystagmograph, Klin Wchnschr **4** 1286 (June 25) 1925, Die Hebelnystagmographie Ihre Geschichte, Fehler, Leistungen und Vervollkommung, Arch f Ophth **120** 235, 1928

6 Meyers, I L Electronystagmography A Graphic Study of Action Currents in Nystagmus, Arch Neurol & Psychiat **21** 901 (April) 1929 Fenn, W O, and Hursh, J B Movements of the Eyes When the Lids Are Closed, Am J Physiol **118** 8 (Jan) 1937 Smith, K U, Kappauf, W E, and Bojar, S The Function of the Visual Cortex in Optic Nystagmus at Different Velocities of Movement in the Visual Field, J Gen Psychol **22** 341 (April) 1940

7 Perlman, H B, and Case, T J Nystagmus Some Observations Based on Electrical Method for Recording Eye Movements, Laryngoscope **49** 217 (March) 1939

8 Dodge, R A Mirror-Recorder for Photographing the Compensatory Movements of Closed Eyes, J Exper Psychol **4** 165 (June) 1921 Dodge, R, and Fox, J C, Jr Optic Nystagmus I Technical Introduction, with Observations in a Case with Central Scotoma in the Right Eye and External Rectus Palsy in the Left Eye, Arch Neurol & Psychiat **20** 812 (Oct) 1928 Fox, J C, Jr, and Dodge, R Optic Nystagmus II Variations in Nystagmographic Records of Eye Movements, ibid **22** 55 (July) 1929

9 Linthicum, F H Nystagmography A Method for the Graphic Recording of Nystagmus During and After Turning and of Caloric Nystagmus, Arch Otolaryng **32** 464 (Sept) 1940

10 Peter,[1] p 300

impulses coming from the retinas, the ocular muscles, the labyrinths and the cochlea and by proprioceptive impulses arising from movements of the head or body It is also influenced by impulses arising centrally from the motor cortex Nystagmus may, in most instances, be considered a compensatory reaction of the eyeballs to defective or abnormal impulses arising from any of these sources It may serve many apparent purposes namely, to retain a specific field of vision,[11] i e, to keep the eyes as long as possible in the same position in relation to the visual field, to increase incoming impulses, to aid in ocular fixation, and to assist in orientation in space

If the head moves or if the field of vision moves, the eyes move in the opposite direction in an attempt to remain fixed in the original field, to maintain as long as possible the same position relative to the visual field or to preserve the image of the fixed object on the retina Because of the limited excursion of the eyes, however, the original field cannot be held, and at their maximal deviation the eyes are jerked back to take up a new focus, this is a corrective movement and is too quick to allow for visual apperception These conjugate movements of the eyes constitute the underlying mechanism for the production of nystagmus If the labyrinth on one side is stimulated by repeated movements of the head or body or by some other means, there is a slow movement of the eyes toward one side, again in an attempt to retain the original field of vision The eyes cannot, however, be held in this position, and they are jerked back to take up a new focus in relation to the environment If these movements persist, nystagmus results If, owing to poor macular vision, inadequate visual acuity or inadequate illumination, the impulses focused on the macula are not sufficient to allow adequate perception, the eyes move from side to side in an attempt to increase or reenforce the incoming visual impulses, to find the sharpest image or to achieve adequate fixation, with no relation to movement of the head or of the field of vision Here, also, nystagmus results, but the movements are equal in amplitude and rate toward each side If nystagmus results from the movement of the field of vision or from attempts to increase vision, it is a reflex response to retinal stimulation and may be called an oculocerebral reflex If it results from movement of the head or body or from irritation of the labyrinth, it is a reflex response to vestibular stimulation and may be called a vestibulocerebral reflex Other mechanisms in the production of nystagmus will be described in the discussion of the specific varieties Owing to the integrative action of the various components of the nervous system and their correlation and interdependence, it is often impossible to separate entirely visual, sensory (proprioceptive), vestibular and other factors

The slow movement in rhythmic nystagmus is the compensatory one and is of primary importance from the functional point of view This component is said to be of peripheral or vestibular origin Its purpose is to preserve the image of the fixed object on the retina The reflex arc involves the labyrinths, the vestibular nuclei, the medial longitudinal fasciculus, the nuclei of the extraocular muscles and the ocular muscles themselves The rapid phase is often referred to as the cerebral, or central, component It has been observed to disappear during anesthesia and to return with the return of consciousness Fox and Holmes[12] placed the reflex center of "optic nystagmus," and therefore the center regulating the rapid component of nystagmus, in the occipital lobe, with communications to the second frontal convolution McIntyre[13] stated that the rhythm of nystagmus is entirely central in origin and is independent of impulses from the ocular muscles, and Meyers[14] observed that the quick component was abolished by lesions in that portion of the motor cortex which is concerned with ocular movements Wilson and Pike[15] found that the quick component of labyrinthine nystagmus was abolished by experimental complete removal of the cerebrum in dogs and cats, provided such removal included the optic thalami Ivy,[16] however, stated that the quick component is not dependent on the integrity of a cerebral reflex arc but, rather, has its center below the thalamus, on which the cerebrum has inhibitory influences It is now known that nystagmus persists after extirpation of the hemispheres, and even after section of

11 McNally, W J Nystagmus, Graduate Lecture, Course no 326, American Academy of Ophthalmology and Otolaryngology

12 Fox, J C, and Holmes, G Optic Nystagmus and Its Value in the Localization of Cerebral Lesions, Brain **49** 333 (Sept) 1926

13 McIntyre, A K The Quick Component of Nystagmus, J Physiol **97** 8 (Nov 14) 1939

14 Meyers, I L Nystagmus Neuro-Otologic Studies Concerning Its Seat of Origin, Am J M Sc **169** 742 (May) 1925

15 Wilson, J G, and Pike, F H The Mechanism of Labyrinthine Nystagmus and Its Modifications by Lesions in the Cerebellum and the Cerebrum, Arch Int Med **15** 31 (Jan) 1915

16 Ivy, A C Experimental Studies on the Brain Stem II Comparative Study of the Relation of the Cerebral Cortex to Vestibular Nystagmus, J Comp Neurol **31** 1 (Oct) 1919

the brain stem to the level of the nucleus of the oculomotor nerve [17] It has been shown that the only part of the central nervous system essential for the production of the slow and quick phases of nystagmus is that portion situated between the oculomotor nuclei, above, and the vestibular nuclei below [11] Spiegel placed the center for the quick component within the vestibular nuclei and regarded these nuclei as the site of origin of both the slow and the rapid component of nystagmus [18] Lorento de No [19] expressed the opinion that there is a rhythmic center situated within the vestibular area, probably in the reticulate substance, the intactness of which is essential to the quick phase, but Spiegel and Sommer [18] asserted that such a center is not necessary and stated that both the slow and the quick phase have their origin in the vestibular nuclei and that the rhythm is dependent on reciprocal inhibition and a refractory phase

Other parts of the nervous system may, however, exert a profound influence on the nystagmus The center for the volitional control of conjugate ocular movements, situated in the caudal portion of the middle frontal gyrus (area 8 $\alpha\beta\delta$), sends fibers through the internal capsule and the cerebral peduncle, from whence they descend with the aberrant pyramidal fibers [20] They probably reach the nuclei of the ocular nerves in the midbrain and pons through the medium of the medial longitudinal fasciculus [21] The zone immediately surrounding the area striata, corresponding to fields 18 and 19 of Brodmann, is the cortical center for optically induced ocular movements and optic fixation reflexes Corticofugal fibers from this center pass through the posterior limb of the internal capsule to the superior colliculus (anterior quadrigeminal body) and thence through the medial longitudinal fasciculus to the nuclei of the ocular nerves Through the latter pathway the optomotor fibers also have connections with the vestibular nuclei, the accessory nuclei and nuclear centers in the upper cervical portion of the cord There are also association pathways from the occipital to the frontal cortical areas, with radiation of optomotor impulses to the frontal cortex, before they descend to the brain stem It may be that the pathways from the cortex that have to do with conjugate ocular movement pass through the vestibular nuclei before they synapse with the nuclei of the ocular nerves Through the aforedescribed mechanisms, impulses for volitional and reflex controls not only bring about conjugate ocular movements but are of importance in the production or inhibition of nystagmus [22]

Nystagmus has long been known, but its significance has not been adequately appreciated and its manifestations have not been classified Even the nomenclature is etymologically incorrect, since the word "nystagmus," as directly translated from the Greek word *νυσταγμος*, means "drowsiness" This noun is derived from the verb *νυσταξω*, which means "to doze," "to be half-asleep," implying, perhaps, "to nod off to sleep" [23] The notion of nodding or jerking could be present in the derivative noun but is absent in the direct translation Authors and textbooks differ in classification and interpretation The terminology is often confusing Clinicians, in referring to rhythmic nystagmus, usually name it from the direction of the rapid component, as this movement is more readily noticed and is more striking The slow phase, however, represents the more active physiologic determinant and is therefore the primary movement, and in writings of experimental workers, anatomists and physiologists, the nystagmus is named after this phase It would be better if the latter terminology were accepted by all or if the direction were qualified when noted

There is a lack of integration of scattered facts regarding the phenomenon, both as it appears in normal persons in response to certain types of stimulation and as it is observed clinically as an expression of disease of the central nervous system, the eyes or of the ear [23] Nystagmus is spoken of as being physiologic or pathologic but these terms are only relative in significance, and the so-called physiologic varieties may be evidenced in the presence of diseases of the nervous system, whereas the so-called pathologic varieties do not always imply the presence of a significant disease process Nystagmus is also often classified as being of ocular, vestibular or neurologic (or central) origin, but these terms are generalities and do not adequately explain the underlying processes Nystagmus may be induced clinically or experimentally by certain tests or methods of stimulation This is called induced, or experimental, nystagmus and is usually a physiologic phenomenon Other varie-

17 Duke-Elder,[2] p 631

18 Spiegel and Sommer,[8] p 77

19 Lorente de No, R The Regulation of Eye Positions and Movements Induced by the Labyrinth, Laryngoscope **42** 233 (April) 1932

20 German, W J, and Fox, J C, Jr Observations Following Unilateral Lobectomies, A Research Nerv & Ment Dis, Proc **13** 378, 1932

21 Walsh, F B Certain Abnormalities of Ocular Movements Their Importance in General and Neurologic Diagnosis, Bull New York Acad Med **19** 253 (April) 1943

22 Spiegel and Sommer,[8] p 411

23 Fox, J C, Jr Nystagmus, Yale J Biol & Med **1** 224 (March) 1929

ties are caused by disease or irritation of any of the structures concerned with vision, ocular movement or equilibrium Such nystagmus is spontaneous and is of clinical significance There may, however, be mixed forms and irregular types of each Any classification of nystagmus is subject to criticism, as it must be somewhat arbitrary and subject to exceptions, but classification is justifiable if it aids in the interpretation of the phenomenon and adds to one's knowledge of the significance of the manifestation The following classification is presented for the sake of clarity, as it seems to correlate fairly effectively the many varieties It is realized, however, that there are discrepancies in the terms, and they must be considered as relative, and not exclusive Furthermore, the classification must not be considered as an etiologic one, and it is presented principally as a basis for further study Later knowledge regarding the mechanism of the phenomenon, the site of origin of the component parts, and other factors, may radically alter it

INDUCED NYSTAGMUS

This type of nystagmus is produced clinically or experimentally by certain tests or methods of stimulation The resulting varieties are usually considered physiologic, and they may be induced in normal persons Changes in the responses, however, occur with disease processes

1 *Optokinetic Nystagmus*—This variety of nystagmus has been known by a variety of names Fox and Holmes[12] and many others have referred to it as optic nystagmus, others have used the terms optokinetic, optomotor or optico-motor It is elicited when a drum or an umbrella painted with vertical stripes is rotated rapidly in front of the eyes or when a person in a rapidly moving vehicle directs his eyes toward fixed objects It is sometimes called railway, or elevator, nystagmus It is a conjugate or conjunctive response of the eyes to a succession of moving visual stimuli The nystagmus is fine, rapid and rhythmic, and it is usually horizontal in direction, depending on the direction of the movement of the body or of the moving object, if the drum is held and moved horizontally, the nystagmus is vertical When a rotating drum is used, the slow phase is in the direction of the movement of the drum, and the quick phase is in the opposite direction When the subject is in a train, the slow phase is in the direction of the moving field of vision,[12] and the quick phase is in the direction in which the subject is moving Thus, the slow phase seems to indicate the pursuit of the moving object,[24] with a quick return in an attempt at fixation on a new, oncoming object The response is intensified if the subject looks in the direction of the quick phase When the subject attempts to fix the eyes on a series of objects moving past in rapid succession, the object is followed until its successor is in the field of consciousness As the image of each successive object falls on the periphery of the retina, the eye is at once moved reflexly with a jerk in an attempt to bring the new object into the macular field This phenomenon is a reflex response to retinal stimulation or to proprioceptive impulses from the muscles of the eye and has been believed to be cortical in origin, probably representing a cortical or an oculocerebral reflex

Opticokinetic nystagmus is a physiologic response, and its absence must be regarded as pathologic Fox and Holmes[12] found it to be lost to the opposite side with lesions of the temporal and parietal lobes, between the visual cortex and the second frontal convolution It has also been found to be absent in cases of homonymous hemianopsia, especially when visual objects are moving from the blind to the normal field[23] This loss may be temporary[20] Fox made the observation that lesions in the posterior portion of the hemisphere, particularly in the region of the supramarginal or the angular gyrus or in the adjacent part of the parietal, occipital or temporal lobe, affected opticokinetic nystagmus when the visual objects were moving in a direction toward the side of the lesion[25] In 2 of 5 cases of tumor of the frontal lobe there was also a change in the nystagmus, but the phenomenon was not modified by lesions in the superior portion of the cerebral hemisphere Fox expressed the belief that this change in the nystagmus could not be explained solely on the basis of imperfect recognition and stated that an interruption of the corticofugal pathways at any point along their course disturbs the ocular response to movements toward the side of the lesion He stated that the frontal lobe probably plays a secondary role in the mechanism underlying opticokinetic nystagmus Smith[26] found that removal of the occipital lobes increases the time necessary for inactivation or extinction of opticokinetic nystagmus He expressed the belief that the frontal cortex exerts an inhibiting mechan-

24 Dodge, R, Travis, R C, and Fox, J C, Jr Optic Nystagmus III Characteristics of the Slow Phase, Arch Neurol & Psychiat **24** 21 (July) 1930

25 Fox, J C, Jr Disorders of Optic Nystagmus Due to Cerebral Tumors, Arch Neurol & Psychiat **28**·1007 (Nov) 1932

26 Smith, K U The Effect of Partial and Complete Decortication upon the Extinction of Optic Nystagmus, J Gen Psychol **25** 3 (July) 1941

ism, controlling the responses toward the opposite side Spiegel referred to two types of opticokinetic nystagmus a cortical variety, which is dependent on concentration, and a subcortical, or passive, variety, which is independent of attention and may be found after extirpation of the hemispheres [27] The production of the latter type is dependent on the intactness of the superior colliculi

Inasmuch as opticokinetic nystagmus is a normal response, the rotating drum test is sometimes used to demonstrate feigned or simulated blindness in a malingerer, to diagnose hysterical blindness and to test for the presence of vision in an infant [28]

2 *Labyrinthine Nystagmus*—This type of nystagmus is a physiologic response which follows the stimulation of the semicircular canals by rapid rotation of the body, by spraying the external auditory canal with warm or cold water, by galvanic stimulation or by changes in pressure It is believed that the stimulation sets up a current or lymphokinesis in the endolymph within the semicircular canals and that this, in turn, stimulates the vestibular nerves It cannot be definitely stated, however, whether the endolymph is static in the resting subject and is in motion only on stimulation of the labyrinth, or whether the fluid is bidirectional in the resting subject and becomes unidirectional on stimulation Some authorities express the belief that there is no circulation of the fluid but that a change in pressure of the labyrinthine fluid stimulates the crista ampullaris It is generally accepted, however, that the movement of the endolymph completely and consistently explains and accounts for the phenomenon The resulting nystagmus is rhythmic Its direction depends on the semicircular canals stimulated, and is thus dependent on the position of the head during stimulation, the direction also varies with the type and intensity of stimulus used It has been stated by some authorities, among these being Favill [29] that each canal apparently has a major control over that pair of ocular muscles which moves the eyes in the plane of the canal Thus, the horizontal canals exert a major control over the internal and external rectus muscles, the anterior vertical canals, over the superior and inferior oblique muscles, and the posterior vertical canals, over the superior and inferior rectus muscles It is probable, however, that each labyrinth, directly or indirectly, has connections with all the ocular muscles of each eye through the medium of the medial longitudinal fasciculus, without a special relationship between canals and muscles [30]

The slow phase of the nystagmus is said to be the resultant effect of the stimuli caused by the movement of the endolymph in the semicircular canals of the labyrinth The head and eyes, and sometimes the body, are deviated in the direction of the endolymph current, and the slow phase of the nystagmus corresponds The rapid phase, after which the nystagmus is often named, is in the opposite direction The excitation of a single semicircular canal produces nystagmus only in a plane parallel with the plane of that canal (Flourens' law), and the relation between the direction of the flow of the endolymph and the direction of the nystagmus is a definite and constant one Reversal of the flow of the endolymph causes a reversal of the direction of the nystagmus Stimulation of more than one canal produces a more complex type of nystagmus It is stated that a horizontal semicircular canal is maximally stimulated by a movement of the endolymph within the canal toward its ampulla, and a vertical canal is maximally stimulated by a movement of the endolymph away from the ampulla (Ewald's first law) Furthermore, maximal stimulation of a semicircular canal results in nystagmus with the rapid component toward the stimulated side while minimal stimulation causes nystagmus with the rapid component toward the opposite side (Ewald's second law [11])

(*a*) Rotational Nystagmus This type of nystagmus is produced by use of the Bárány chair The subject is rotated rapidly, about ten times in twenty seconds, and the rotation is then abruptly stopped The head is held fixed by a head rest, and the eyes are closed to prevent the development of opticokinetic nystagmus At the beginning of rotation, owing to inertia, the endolymph moves less rapidly than does

27 Scala, N P, and Spiegel, E A Subcortical (Passive) Optokinetic Nystagmus in Lesions of the Midbrain and of the Vestibular Nuclei, Confinia neurol **3** 53, 1940

28 Snell, A C The Optokinetoscope, Tr Am Acad Ophth **44** 396, 1939

29 Favill, J The Relationship of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus, Chicago, Privately Printed, 1936, An Explanation of the Mechanism of Induced Rotary and Vertical Nystagmus, Arch Neurol & Psychiat **13** 479 (April) 1925, The Twenty-Six Normally Possible Forms of Rotationally Induced Nystagmus, ibid **19** 318 (Feb) 1928

30 Barany, R The Relationship Between Semicircular Canals and the Eye Muscles The Central Mechanism in Vestibular Nystagmus, in Transactions of the Ninth Otological Congress, 1912, pp 592-595 Quix, F H The Function of the Vestibular Organ and the Clinical Examination of the Otolith Apparatus, J Laryng & Otol **40** 425 (July), 493 (Aug) 1925

the body, and there is an apparent movement in the direction opposite the direction of the body As a consequence, during rotation, the eyes are drawn to the opposite side, and the slow phase of the nystagmus is opposite the direction of rotation, with the recovery jerks, or the rapid phase, in the direction of rotation When the rotation ceases abruptly, the momentum of the labyrinthine fluid causes it to continue to move in the direction of the recently completed movement of the body, even though the head is now stationary [31] This causes the after-nystagmus, which is what one observes clinically, and it is opposite in direction to the primary nystagmus The movements of the head, body and eyes, including the slow phase of the nystagmus, are in the direction of the recently completed rotation, whereas the rapid phase is in the opposite direction In rotation tests, the nystagmus described is usually the after-nystagmus Depending on a number of factors, including the rate and duration of the rotation and the sensitivity of the labyrinthine apparatus, the examiner may observe past pointing or kinetic deviation and postural deviation or falling, and the subject may also experience vertigo, nausea and vomiting, and sometimes even diaphoresis, prostration and shock The direction of the nystagmus depends on the semicircular canal or canals that are stimulated If the head is tilted forward 30 degrees, so that the horizontal canals are in the horizontal plane, horizontal nystagmus will result If the head is tilted forward 90 degrees, backward 60 degrees or laterally 90 degrees, the vertical canals will be stimulated, and rotatory, or vertical, nystagmus will result Diagonal and mixed nystagmus is produced by stimulating more than one set of canals

(*b*) Thermal or Caloric Nystagmus This form of nystagmus is produced by douching the external auditory canals with hot water (40 to 45 C, or 104 to 113 F) or cold water (20 to 21 C, or 68 to 70 F) or by introduction of hot or cold air A more prompt response may be obtained with the use of ice water (0 to 10 C, or 32 to 50 F) It is said that the change in the temperature of the endolymph causes it to circulate and that only those canals which are in the vertical plane are affected Cold water causes the endolymph to flow from above downward and toward the side stimulated, whereas hot water has the opposite effect Some authorities, however, doubt the production of a thermal current in the endolymph and state that the hot or cold water may stimulate the labyrinth directly or, through vasomotor changes, may cause an increase or a fall in labyrinthine pressure Possibly the vestibular endings are stimulated directly if the water is too hot or too cold, and there may be an associated change in the tonus of the otolith organs secondary to the change in the temperature [32] If the patient is examined in the prone position with the head tilted 30 degrees forward, or in the seated position with the head tilted forward 90 degrees or backward 60 degrees, the horizontal canals are vertical in direction and can be stimulated, with resulting horizontal nystagmus, if the subject is lying supine with the head tilted forward 90 degrees or backward 60 degrees, or is seated with the head tilted forward 30 degrees, the anterior vertical canals are stimulated, with resulting rotatory nystagmus The posterior vertical canal is too far distant from the middle ear for stimulation in this test With the use of cold water, the slow phase of the nystagmus, as well as the past pointing and postural deviation, will be toward the side stimulated, while the recovery jerks, or the rapid phase of the nystagmus, will be in the opposite direction Hot water will produce the opposite effects

(*c*) Nystagmus Induced by Galvanic Stimulation The vestibular endings are probably stimulated directly and the movement of the endolymph in the semicircular canals is not ordinarily affected When the anode is used as the stimulus, the slow phase will be toward the side stimulated, and with the cathode the opposite response is obtained Inasmuch as a strong current is sometimes followed by an after-nystagmus, it is possible that the electrical stimulus may also cause movement of the endolymph

(*d*) Compression Nystagmus Unilateral changes in pressure in the semicircular canals by means of the experimental introduction of a pipet manometer into one of them or by alterations in the pressure of the middle ear by such factors as infection may produce nystagmus An increase in pressure causes nystagmus with the slow phase to the opposite side, and a decrease in pressure results in nystagmus with the slow phase to the same side [33]

Comment: Labyrinthine, or vestibular, nystagmus is a reflex response to movements of the head or body or to stimulation of the labyrinth and is thus a vestibulocerebral reflex Pathologic variations of the response may accom-

31 Duke-Elder,[2] p 633

32 Mygind, S H: How Does Caloric Nystagmus Arise? J Laryng & Otol **40**:444 (July) 1925

33 Fischer, J, and Wolfson, L E The Inner Ear, Including Otoneurology, Otosurgery, and Problems in Modern Warfare, New York, Grune & Stratton, Inc 1943, p 86

pany disease processes, and modifications may be produced by experimental means An unequal response on the two sides, a perversion of response or a dissociation of response with vertigo and past pointing but without nystagmus, all indicate lesions of the vestibular centers or their central connections With lesions of the brain stem, one may find absence of response from one set of canals with preservation of the response from the other canals It is stated that the reflex process is independent of all impulses or activities other than the afferent path from the labyrinth, the nuclei of the muscles concerned and a single efferent motor path However, ocular inhibition in animals may change or decrease the labyrinthine nystagmus,[31] and it is entirely possible that proprioceptive impulses arising from the body or the cerebellum, other than those conveyed through the vestibular system, and possibly proprioceptive impulses from the ocular muscles, may alter the response The part that the semicircular canals play in the reflex is not known, and rotational vestibular nystagmus may be produced with the semicircular canals tied off at the ampullae The cerebral cortex also influences vestibular nystagmus, and voluntary movements of the eyes toward the side of the quick component accentuate the response After the removal of one temporal lobe or cerebral hemisphere, experimental labyrinthine nystagmus with the slow component toward the side opposite the lesion is more easily elicited and of greater intensity than is that with the slow phase toward the involved side It has been stated that the directional predominance (*Nystagmusbereitschaft*) is toward the extirpated side, but this refers to the quick component of the nystagmus[34] The nystagmus may be diminished when the slow component is directed toward the side of the lesion[35] The cerebrum does not enter into the reflex arc of labyrinthine nystagmus, but it does exert an inhibitory control over the reflex The cerebellum may also have an inhibitory effect on labyrinthine nystagmus, and this inhibition is reduced with cerebellar lesions Pigeons with cerebellar lesions do not become habituated to labyrinthine nystagmus as readily as do controls[36] Acrobats, dancers, aviators and persons who are employed in work requiring rapid movements of the body in space have a reduced labyrinthine nystagmus The nystagmus that results from vestibular stimulation may be diminished, and even extinction can be produced, by repeated rotations of the body This is probably not the result of pathologic changes in the nervous system that are produced by the repeated rotations, and the diminished nystagmus does not interfere with equilibration but may even aid it That dancers, for example, who have diminished nystagmus, and animals in which the nystagmus has been reduced by repeated rotations of the body have what appears to be better equilibrium than normal may be due to the fact that postural and kinetic deviation and the somatic and visceral effects of rotation, such as nausea, are also reduced, and these manifestations are incompatible with muscular coordination and equilibrium[37]

3 *Reflex Acoustic Nystagmus*—Rhythmic nystagmus results from loud auditory stimuli The quick component is toward the side of the stimulus

4 *Reflex Sensory Nystagmus*—Rhythmic nystagmus follows stimulation of the skin in the neighborhood of the ear on pressure on the tragus Here, also, the quick component is toward the side of stimulation Handling of the eyelids during examination may also produce a reflex sensory nystagmus

5 *Chemical or Toxic Nystagmus*—Nystagmus is known to result from the use of drugs and from association with various toxins (see page 55) Chemical stimulation can also be used to produce experimental or induced nystagmus Pentobarbital injected intravenously in rabbits produces a nystagmus of long duration, which appears at the initiation and at the cessation of narcosis[38]

PATHOLOGIC VARIETIES OF NYSTAGMUS

These forms of nystagmus, in most instances, indicate the presence of an abnormal process in the eyes, the ocular muscles or the central connections concerned with ocular movement or

34 De Kleyn, A Some Remarks on Vestibular Nystagmus, Confinia neurol **2** 257, 1939 Fitzgerald, G, and Hallpike, C S Studies in Human Vestibular Function I Observations on the Directional Preponderance ("Nystagmusbereitschaft") of Caloric Nystagmus Resulting from Cerebral Lesions, Brain **65** 115 (June) 1942

35 Wilson and Pike[15] Ivy[16]

36 Halstead, W , Yacorzynski, G, and Fearing, F Further Evidence of Cerebellar Influence in the Habituation of After-Nystagmus in Pigeons, Am J Physiol **120** 350 (Oct) 1937

37 Yacorzynski, G K , Halstead, W, and Fearing, F Relationship Between the Experimental Reduction of Vestibular Nystagmus and Equilibrium, J Psychol **11** 161 (Jan) 1941

38 Kisch, B A New Method to Produce Nystagmus, Exper Med & Surg **1** 169 (May) 1943

bodily equilibrium They are spontaneous, not induced, and are usually of clinical significance

1 *Nystagmus Originating in the Eye or Its Adnexa*—(*a*) Nystagmus of Optic Derivation The varieties of nystagmus in this group result from deficient vision, due either to impaired visual acuity or to inadequate illumination and retinal fatigue The nystagmus is pendular rather than rhythmic in character, and the movements appear to result from an attempt to maintain fixation of vision in spite of deficient acuity or insufficient light The nystagmus may appear in early infancy or may be acquired It is not congenital in the sense of true congenital or hereditary nystagmus, to be described later

(1) "Ocular" Nystagmus This is of the pendular variety and is usually coarse and slow The nystagmus is characterized by to and fro movements, often of equal range and velocity, toward each side of a central point The movements may be wide and aimless and of the "wandering" or "roving" type They may be quite irregular They are usually horizontal, occasionally vertical and rarely rotatory This type of nystagmus is seen in persons who have had very deficient vision since birth, in persons whose vision has failed before fixation is learned, in persons whose fixation is deficient, in color-blind persons or in persons with increased sensitivity to light It is observed principally in persons with congenital cataract, ophthalmia neonatorum, interstitial keratitis, congenital corneal leukoma, chorioretinitis, high errors of refraction, especially high grade myopia, and albinism The nystagmus develops shortly after birth, and it does not occur in persons who are blind from birth It probably begins when the infant first attempts fixation As a result of poor vision or imperfect macular vision, a "searching" movement of the eyes develops as the infant attempts to increase the incoming impulses, to find the sharpest image or to achieve adequate fixation It is an adaptation to attain fixation in spite of defective vision Sometimes there is an associated nodding of the head It does not occur in adults unless macular vision is disturbed, and when the blindness is acquired later in life the movements are slower, wider in range and seemingly aimless, they are less rhythmic and probably do not constitute a true nystagmus, but they, also, represent attempts at fixation Ocular nystagmus has been classified as that associated with amblyopia and that resulting from amaurosis, but there is no nystagmus associated with complete blindness Unilateral nystagmus may occur with unilateral atrophy of the optic nerve or with other visual defects An inconstant spontaneous nystagmus is sometimes seen with homonymous hemianoptic visual defects, particularly when the subject is looking to the blind side This is probably not entirely ocular in origin, as it is usually of the rhythmic type and may vary with position Some authorities believe that there may be a nystagmus associated with refractive errors without serious loss of vision

(2) Occupational Nystagmus This form results from eye strain due to deficient illumination, repeated movements of the eyes or retinal fatigue It is a pendular nystagmus, fine in degree, rapid in rate, often vertical in direction and increased on upward gaze The movements may not be conjugate Fixation is also defective, and there may be spasm of the levator palpebrae superioris muscle Occupational nystagmus is most frequently encountered in miners and other persons who work in poor light, and it is commonly referred to as "miner's nystagmus" It is also seen in compositors, draftsmen, jewelers, train dispatchers, crane workers, painters and others whose work necessitates movement of the eyes and strain on the ocular muscles or results in retinal fatigue [39] It most often develops after long exposure to poor illumination, especially after working in a stooped attitude with the eyes deviated upward, and is probably the result of insufficiency of binocular fusion Only the rods are used for vision in imperfect light, and as there are no rods at the macula there is inefficient macular vision in poor illumination As a result there is a constant shifting of the axis of the eyes After a time this shifting is present constantly, and not only in dim light It is possible that there may be an associated vestibular component, inasmuch as the movements may be influenced by a change in the position of the head [40] Some workers regard the phenomenon as a true neurosis, a result of "neuromotor exhaustion," and others postulate fatigue and toxic factors as of etiologic import It may be that neurotic factors play a part in maintaining the nystagmus or in the production of symptoms, but deficient illumination, together with strain on the ocular muscles and retinal fatigue, seems to explain the phenomenon Improved lighting, improved working conditions or cessation from work for

39 (*a*) Spicer, W T H, in Discussion on Nystagmus, Proc Roy Soc Med (Sects Neurol, Ophth & Otol) **7** 20, 1913-1914 (*b*) Smith, H C, and Riesenman, F R Unusual Forms of Nystagmus, with a Review of the Literature, Arch Ophth **33** 13 (Jan) 1945

40 Duke-Elder,[2] p 639

a time may result in disappearance of the nystagmus, except the most severe form

(3) Spasmus Nutans This condition is seen in babies from 6 months to 2 years of age It consists in rhythmic nodding or rotatory tremor of the head accompanied with a fine, rapid, pendular type of nystagmus The nystagmus is usually horizontal in direction, but it may be vertical The movements may be unilateral or dissociated Closing of the eyes stops the tremor and the nystagmus, while forceful control of the tremor increases the nystagmus The condition has been ascribed to rickets, but it is known to occur in children who live in dark dwellings where no sunlight penetrates, regardless of the presence of rickets The condition may be of complex origin, both ocular and central, but the cessation of the nystagmus on closing the eyes suggests that there is an ocular element in the causation of the disorder, perhaps similar to that in miner's nystagmus

(4) Reflex Nystagmus This form occurs in the presence of painful disease of the eye, is a pathologic variation of reflex sensory nystagmus and may also be considered to be of ocular derivation

(*b*) Nystagmus of Neuromuscular Origin In a large percentage of normal persons a few fine, rapid nystagmoid movements are seen on extreme deviation of the eyes This is more noticeable on lateral gaze and is usually horizontal in direction The rapid movement is in the direction of gaze and represents intermittent attempts of the agonists to maintain fixation The slow return represents the reflex contraction of the overstretched antagonists in an attempt to return the eyes to the central position [23] These movements are irregular and are usually transient, they may disappear gradually after five to ten jerks This type of oscillation is sometimes referred to as *Endstellungsnystagmus,*[41] or "end position nystagmus," inasmuch as the movement is present only on extreme position of the eyes, but the terms "fixation nystagmus," "positional nystagmus" and "pseudonystagmus" are also used, and some authorities prefer to designate the movements as nystagmoid jerks, as they feel that the movements do not constitute a true nystagmus The term *Endstellungsnystagmus* is not very appropriate, as end position nystagmus may be found with various pathologic states in which the movements are evident only on, or are exaggerated by, deviation of the eyeballs These movements may occur in normal persons when they attempt to fix their eyes on an object without turning the head in the direction of the object or when they suddenly change the field of vision The movements disappear when fixation has been established The nystagmus may be the result of an abnormally great effort to balance the activity of the agonists and the antagonists The tendency toward the phenomenon is increased with fatigue states, paresis of the ocular muscles and abnormal attempts at fixation and is often seen in nervous subjects Exaggerations of this type of nystagmus are seen in the circumstances indicated in the following paragraphs

(1) Paretic Nystagmus This condition develops on the attempt to use a paretic ocular muscle It is a rhythmic nystagmus, which occurs near the limit of the range of movement of a weak ocular muscle When the subject is looking toward the paretic side, the weak agonist pulls the eyeball outward with a rapid jerk to avoid diplopia, and the antagonistic muscles slowly pull the eyeball back to the neutral position There may be dissociation between the movements of the paretic and those of the normal eye One finds such a nystagmus in persons with localized extraocular palsies, but it may also occur with paresis of conjugate gaze

(2) Fatigue Nystagmus This is similar to paretic nystagmus It may follow excessive use of or increased fatigability of certain extraocular muscles or may occur in generalized fatigue states or asthenia It is usually observed only at extremes of lateral gaze and is generally abortive rather than sustained It may occur when a subject attempts to hold his eyes in any extreme position for too long a period In patients with myasthenia gravis one may observe nystagmus, which may be either of the paretic or of the fatigue variety

(3) Nystagmus of Eccentric Fixation This type appears on deviation of the eyes beyond the limits of the binocular visual field It is jerky and rhythmic in type and horizontal in direction It may occur without pathologic significance, and it is said to be present in 50 to 60 per cent of normal persons when the axes of fixation are deviated [42] It is induced more readily by, or increased in, fatigue

(4) Latent Nystagmus This form appears on covering one eye in subjects with poor visual acuity or without binocular vision, especially patients with amblyopia resulting from strabismus It occurs in the covered eye and is in the direction of the open eye [43] Nystagmus of

41 Spiegel and Sommer,[3] p 105

42 Duke-Elder,[2] p 636

43 Duke-Elder,[2] p 638

eccentric fixation and latent nystagmus may be partially of ocular origin, inasmuch as they represent an attempt to aid vision, but the rhythmicity suggests neuromuscular factors in their causation

(*c*) Opticokinetic Nystagmus This form of nystagmus, especially if it is the result of a minimal stimulus, may be considered as a variety either of spontaneous nystagmus of ocular derivation or of nystagmus of neuromuscular origin This illustrates the functional relationship of the various types of nystagmus If the opticokinetic nystagmus is dependent on fixation and results from an attempt to maintain central, or macular, vision or to visualize more clearly the object that is in the field of vision, one may consider it of ocular origin, if it results from attempts at fixation on a moving object, from an effort to keep the eyes in one position or from tension on the ocular muscles, one may consider it of neuromuscular origin While opticokinetic nystagmus is considered a physiologic response, a normal result of fixation of the eyes on moving objects, it may in certain circumstances be a pathologic variety of nystagmus The tendency of certain persons to experience motion sickness, train sickness, air sickness and sea sickness may in part be due to a latent tendency toward the development of opticokinetic nystagmus The related presence of an oversensitive vestibular or labyrinthine apparatus with these varieties of motion sickness indicates, however, that there are other factors than the ocular ones This illustrates further the integrative action of the various portions of the nervous system in the production of nystagmus

2 *Nystagmus Due to Involvement of the Centers Controlling Ocular Movement and Equilibrium*.—This type is, in most instances, true pathologic nystagmus It is of diagnostic import in the presence of many diseases of the central nervous system It must be stated, however, that certain varieties, while not actually physiologic, do not denote the presence of serious disease of the nervous system The nystagmus of this general type is sometimes classified as cerebral (or central), cerebellar and vestibular, but, inasmuch as synthesis of the centers in the cerebrum which regulate ocular movements, the superior colliculus, the cerebellum, the nuclei of the ocular motor nerves, the medial longitudinal fasciculus and the vestibular apparatus is necessary for smooth and coordinated ocular movement, it is not always possible or feasible to differentiate the various subtypes Unfortunately, the many varieties are often classified together as "central" nystagmus, but this terminology tells little regarding the etiologic factors or the site of pathologic change Nystagmus due to involvement of the centers controlling ocular movement and equilibrium is rhythmic and may occur in any direction It is similar in many respects to the induced nystagmus which is produced on stimulation of the labyrinth or the vestibular centers It is of more significance if it is of the mixed or rotatory varieties or if there is dissociation of movement The range and velocity of the movements may vary widely The nystagmus may be spontaneous and present at rest, or it may be present only on fixation, at extremes of gaze or on change of the position of the head or body Peter stated that nystagmus which is not the result of an ocular or an otologic factor is always the result of a lesion of the structures of the brain below the tentorium cerebelli,[44] but this is not true The pathologic process may be in any of the following sites (*a*) the cerebral cortex, especially the centers in the frontal, occipital and temporal regions which control ocular movement, and the central connections of the vestibular system, (*b*) the basal ganglia or the thalamus in certain instances, (*c*) the corticofugal pathways from the oculogyric centers, (*d*) the superior colliculi (anterior quadrigeminal bodies), (*e*) the nuclei of the oculomotor, trochlear and abducens nerve, (*f*) the medial longitudinal fasciculus and its nuclear connections, involving this tract as far caudally as its termination in the cervical portion of the spinal cord, (*g*) the vestibular mechanism, including the labyrinth, the vestibular nerves, the vestibular nuclei and their central connections, and (*h*) the cerebellum and its connections with the spinal cord, the vestibular centers, the brain stem and the cerebrum

(*a*) Vestibular Nystagmus Vestibular nystagmus is a reflex response to stimulation or destruction of the labyrinth The afferent impulse passes from the labyrinth to the area of the vestibular nuclei and thence to the nuclei of the ocular muscles, and the efferent, or motor, path goes to the individual muscles Stimulation of the labyrinth, of specific semicircular canals, of the vestibular nerves or of the vestibular nuclei by a toxic process, pressure, edema or inflammation produces essentially the same type of response as does stimulation of these centers by rotation, heat or cold or the galvanic current, and the response depends on the type of stimulus and the part of the vestibular system that is stimulated It has been stated that the horizontal canals are responsible mainly for horizontal nystagmus, the posterior vertical canals for vertical nystagmus and the anterior vertical canals for rotatory nystagmus Each labyrinth

44 Peter,[1] p 307

has connections with all the ocular muscles of each eye The pathologic process may cause a unidirectional flow of the endolymph, or it may stimulate the nerve endings or the nuclei directly Destruction of one labyrinth or of one vestibular nerve results in a rhythmic, spontaneous nystagmus the slow phase of which is toward the injured side,[28] and there may be associated deviation of the eyes and head toward this side The labyrinths are antagonistic to each other, so that elimination of one acts as a stimulus to the other The amplitude of the nystagmus is increased by turning the eyes in the direction of the quick phase or by the elimination of fixation by placing strong lenses in front of the eyes [23] The direction of the nystagmus may be reversed by altering the position of the head Nystagmus which follows destruction of one labyrinth gradually diminishes and disappears It may last only two or three days and is usually gone in a week, as the loss of one labyrinth is compensated for by processes in the corresponding vestibular nuclei [45] The nystagmus which appears after destruction of one labyrinth disappears if the other labyrinth is rendered functionless

Hemorrhage into the labyrinth, suppuration of the labyrinth secondary to disease of the middle ear, increased or decreased pressure of the labyrinthine fluid, pressure on the inner ear, trauma to the vestibular nerve as a result of skull fracture, intracranial hemorrhage, meningitis, involvement of the vestibular nerve by a neoplastic process, such as a neurinoma of the cerebellopontile angle, or toxic or inflammatory involvement of the labyrinth or the nerve will result in nystagmus, which may be temporary or persistent The nystagmus associated with toxic labyrinthitis may result from stimulation of the vestibular end organs by the toxic process, or it may be of the compression variety, resulting from increased pressure of the labyrinthine fluid in the semicircular canals In patients with Ménière's syndrome the nystagmus may result from increased secretion of the endolymph on an allergic basis, or it may be due to change in the acid-base or the electrolyte balance In patients with disease of the middle ear nystagmus may be produced by sudden compression of the external auditory meatus It may be possible to differentiate between nystagmus due to irritation and that due to destruction of the labyrinth by caloric stimulation of the external auditory canal With the former the nystagmus will be increased, whereas with the latter no reflex nystagmus will be elicited and there will be no change in the nystagmus which is already present With many disease processes, such as tumors of the cerebellopontile angle, multiple sclerosis and lesions of the pons and medulla, vestibular nystagmus may be complicated by the existence of nystagmus due to involvement of the cerebellum, the medial longitudinal fasciculus or other structures

(*b*) Nystagmus of Cerebellar Origin This may be an ocular expression of cerebellar asynergia or ataxia, a result of synergic disorders of fixation of cerebellar origin, it may be due to involvement of the cerebellar connections with the vestibular apparatus, the medial longitudinal fasciculus or higher centers, or it may be a specific manifestation of cerebellar dysfunction Nystagmus is a common symptom in patients with cerebellar lesions, regardless of whether they are traumatic, vascular, degenerative, inflammatory or neoplastic in nature, and it may occur with lesions of the vermis, of the hemispheres, either cortical or subcortical, or of the cerebellar peduncles and their connections With unilateral ablation of the cerebellum in animals, coarse, slow jerks occur when the eyes are directed to the side of the lesion, and rapid and finer jerks, when the eyes are directed to the opposite side With lesions of the cerebellum, the eyes at rest are deviated 10 to 30 degrees toward the unaffected side [23] The movements may be present on fixation or on deviation in any direction When the subject attempts to focus on an object directly in front of him, the eyes wander slowly back to the resting position and are returned to the midline by means of quick jerks On his looking toward either side, there are quick jerks toward the point of fixation with slow return movements to the resting point The rapid movements are always in the direction of gaze, and the slow movements are toward the position of rest The nystagmus is always more pronounced when the subject is looking toward the side of the lesion

It has often been stated that nystagmus develops in patients with cerebellar lesions only as a result of the effect of the lesion on the vestibular centers through pressure and edema, but this obviously is not the case It may be that the cerebellum has an inhibitory effect on nystagmus, inasmuch as the phenomenon develops after ablation of the cerebellum and removal of one hemisphere results in an increase in nystagmus toward the side of the lesion Spiegel produced vertical nystagmus by means of lesions in the nodulus or other parts of the vermis He expressed the belief that this may be the result of the release of the vestibulo-ocular reflex arcs from cerebellar inhibition [45] Pigeons with cerebellar lesions do

45 Spiegel, E A, and Scala, N P The Significance of Nystagmus in Differential Diagnosis, with Special Reference to Vertical Nystagmus, Tr Am Therap Soc **42** 60, 1942

not become habituated to nystagmus as readily as do controls [36] It is probable, however, that irritation of this portion of the central nervous system also produces nystagmus The exact site of damage is often difficult to determine because of the multiplicity of connections with the vestibular, oculogyric and other centers It is said that cerebellar nystagmus is dependent on fixation, in contrast to vestibular nystagmus, which is increased when fixation is eliminated by the use of strong lenses [23] In vestibular nystagmus the slow phase is toward the injured side, while in cerebellar nystagmus the slow phase depends on the position of the eyes [23]

(*c*) "Central" Nystagmus "Central" nystagmus may result from lesions of the oculogyric centers in the frontal, occipital or temporal lobe, central involvement of vestibular function in the temporal lobe, or involvement of the descending pathways from the volitional oculogyric center in the frontal lobe or of the corticofugal fibers from the occipital lobe, the medial longitudinal fasciculus and its connections or the nuclei of the nerves which control ocular movement It may vary in type, degree, rate and direction but is always of the rhythmic variety With central lesions there is often a dissociation of movement, with unequal nystagmus on the two sides or with unilateral nystagmus This is especially true if the disease process is in the brain stem Spontaneous vertical nystagmus is said to be characteristic of intracranial disease because it is dependent for its production on the simultaneous stimulation of both posterior or of both anterior vertical semicircular canals, or of the pathways connecting them, the last-named being the most likely site It has been stated that spontaneous vertical nystagmus is an infallible and pathognomonic sign of a pathologic lesion of the brain,[46] although Spiegel and Scala [47] produced such nystagmus by peripheral labyrinthine lesions

Cerebral lesions may cause spontaneous nystagmus, or they may influence or alter the induced opticokinetic or labyrinthine nystagmus In patients with cerebral lesions the nystagmus is usually of the fixation type and is probably an exaggeration of positional nystagmus when the eyes are deviated away from the side of the lesion [23] An inconstant nystagmus is sometimes seen with homonymous hemianoptic defects, particularly when the subject is looking to the blind side It has been stated that cerebral lesions, especially if destructive, may abolish the quick phase of the nystagmus, but it is now known that the quick phase is not necessarily a cerebral function In most instances cerebral nystagmus is the result of suspension of the inhibitory action of the cortex on the centers of ocular movement [48] For localization of the lesion that causes nystagmus of a central type, one must rely on associated signs and symptoms Associated paresis of upward gaze may suggest mesencephalic involvement, while conjugate paresis of lateral gaze may suggest cortical or pontile involvement Paresis of conjugate lateral gaze with associated paralysis of individual muscles places the lesion near the nuclei of the cranial nerves involved

Nystagmus that results from involvement of the supranuclear or association pathways is found with many diseases of the nervous system, among which may be mentioned multiple sclerosis, Friedreich's ataxia, Marie's hereditary ataxia, olivopontocerebellar atrophy, syringobulbia, syringomyelia and vascular, neoplastic or degenerative diseases of the brain stem It is often impossible to state whether the primary disease process is cerebral or is in the brain stem, the cerebellum or the connecting pathways, and in many instances, as in encephalitis, multiple sclerosis and toxic processes, it is disseminated Harris has recently described an "ataxic nystagmus" which he states is a pathognomonic sign of multiple sclerosis [49] When the eyes are turned laterally, it is seen that the conjugate action is weak, and the opposite eye does not reach the inner canthus The eye on the side toward which the eyes are being turned shows a coarse nystagmus, with the quick movement in the direction of gaze and a slow return movement The nystagmus continues as long as the eyes are deviated This type of nystagmus may be unilateral, it may be present on looking in either direction, or it may be disproportionate The nystagmus associated with multiple sclerosis may, however, vary greatly in individual cases, depending on the site of the pathologic change

3 *Miscellaneous Varieties of Nystagmus*—(*a*) Toxic Nystagmus This type may be associated with definite disease of the nervous system, but oftentimes it is the only objective manifestation of the ingestion of certain drugs, especially the barbiturates,[38] acetanilid and related drugs, diphenylhydantoin, lead, nicotine, chloroform,

46 Fisher, L, and Glaser, M A New Vestibular Complexes for Localization of Brain Lesions, Arch Neurol & Psychiat **21** 876 (April) 1929

47 Spiegel, E A, and Scala, N P Vertical Nystagmus Produced by Peripheral Labyrinthine Lesions, Arch Otolaryng **40** 160 (Sept) 1944

48 Rea, R L Neuro-Ophthalmology, ed 2, St Louis, C V Mosby Company, 1941, p 67

49 Harris, W Ataxic Nystagmus A Pathognomonic Sign in Disseminated Sclerosis, Brit J Ophth **28** 40 (Jan) 1944

quinine and alcohol It is also found during the febrile state of acute infectious diseases The site of the damage may vary With toxic labyrinthitis it is localized to the labyrinths, but the toxic process may involve other parts of the nervous system The nystagmus that is seen in persons with epilepsy may be a result of the disease process underlying the convulsive disorder, or it may be a toxic nystagmus, a result of the anticonvulsant medication

(*b*) Congenital or Hereditary Nystagmus This form, which dates from birth, must be differentiated from ocular nystagmus, which does not develop until fixation is attempted Furthermore, it is rhythmic and more rapid and is not associated with defective vision It may be inherited along mendelian lines and is probably the result of a congenital abnormality or hypoplasia of the central nervous system It has been stated that hereditary nystagmus may be an autosomal recessive trait, it may be sex linked, occurring only in males; or it may be irregularly dominant occurring in both sexes [50] It may be associated with partial albinism

(*c*) Nystagmus Due to Involvement of the Cervical Portion of the Spinal Cord The lesion is usually above the fourth cervical segment, as in cases of syringomyelia and tumors of the cervical part of the cord The nystagmus is "central" in that it indicates involvement of the medial longitudinal fasciculus or the spinocerebellar or vestibulospinal pathways There may be some relationship between the tonic neck reflexes and their effect on ocular movement and the nystagmus which results from cervical lesions

(*d*) Hysterical Nystagmus Many authorities have described hysterical varieties of nystagmus The actual existence of such a type is to be doubted, but if it does occur it may be the result of inadequate neuromuscular control of the lateral movements of the eyes and failure of alternate contraction of the agonists and antagonists on deviation of the eyes The movements are usually described as jerky and irregular, but they may be pendular [51] They may be brought on by emotional strain, but it must be borne in mind that a true pathologic nystagmus may be increased by nervous tension and that nervous and fatigued persons are especially apt to show nystagmoid movements or fixation nystagmus when they attempt to fix their eyes on some object with extreme deviation With so-called hysterical nystagmus there may be associated spasm of the orbicularis oculi and medial rectus muscles

(*e*) Voluntary Nystagmus Such a form has also been described and nystagmus can occasionally be simulated Voluntary nystagmus is usually pendular and it may be unilateral or bilateral [39b] The movements are extremely rapid, they are usually horizontal but may be in any direction The movements are increased by fixation, by convergence or by increasing the width of the palpebral fissure [52] The nystagmus disappears when the subject's attention is distracted or when vision is blurred by a convex lens placed in front of each eye The movements are said to be produced at will and they are not associated with any pathologic entity It is doubtful whether these voluntary movements of the eyeball should be considered as a type of nystagmus

University Hospital

50 Allen, M Primary Hereditary Nystagmus Case Study with Genealogy, J Hered **33** 454 (Dec) 1942

51 Smith and Riesenman [39b]

52 Unsworth, A C A Discussion of Ocular Malingering in the Armed Services, Am J Ophth **28** 148 (Feb) 1945

ONSET OF GUILLAIN-BARRÉ SYNDROME FOLLOWING EXPOSURE TO MUSTARD GAS

CAPTAIN JOSEPH G CHUSID
AND
COLONEL GILBERT H MARQUARDT
MEDICAL CORPS, ARMY OF THE UNITED STATES

The clinical incidence of neurologic sequelae of mustard gas poisoning or exposure is rare Mustard gas, the popular name of dichloroethyl sulfide, was known during World War I as "king of battle gases," [1] inasmuch as, pound for pound, it produced nearly eight times the number of casualties produced by all the other battle gases combined Marshall [2] concluded that systemic effects occurred in animals, due in part to absorption of mustard gas or a hydrolytic product thereof, when these animals were poisoned by inhalation, injection or cutaneous application of this substance Winternitz [3] stated that animals which died in the acute stage, before the development of extensive pneumonia, probably succumbed as a result of the combined effects of destructive changes in the lung and systemic effects from absorption of the gas Warthin [4] mentioned the following signs referable to the central nervous system in animals exposed to mustard gas vapor increased reflex excitability, tremors, convulsions, marked depression, stupor and coma His examination of the brain and spinal cord of rabbits and of 1 human being disclosed congestion and edema throughout Gilchrist and Matz [5] reviewed the clinical status of 89 persons living who had previously been exposed to mustard gas during World War I and of 53 who had died as a result of such exposure and concluded that mustard gas affected particularly the skin, the mucous membranes of the upper portion of the respiratory tract and the eyes and their appendages and that secondary bronchopneumonia was a frequent complication and cause of death following mustard gas poisoning No organic neurologic sequelae were noted

The term Guillain-Barré syndrome has been used to designate that type of polyneuritis occurring with albuminocytologic dissociation and characterized clinically by acute onset, mild or no febrile reaction, radicular neuritis, palsy of the cranial nerves and muscular tenderness [6] The syndrome has been called by others acute infectious polyneuritis,[7] polyneuritis with facial diplegia,[8] polyradiculoneuritis,[9] infectious neuronitis [10] and myeloradiculitis [11] Attempts to isolate or identify the infectious agent have generally been unsuccessful [12] The possible rela-

From the Neurology Section of the Medical Service, AAF Regional and Convalescent Hospital, Miami District, Miami Beach, Fla

1 Prentiss, A M Chemicals in War, New York, McGraw-Hill Book Company, Inc, 1937

2 Marshall, E K, Jr Physiological Action of Dichloroethyl Sulphide, in Ireland, M W The Medical Department of the United States Army in the World War Medical Aspects of Gas Warfare, Washington, D C, Government Printing Office, 1926, vol 14, p 369

3 Winternitz M C Pathology of War Gas Poisoning, New Haven, Conn, Yale University Press, 1920

4 Warthin, A S Pathologic Action of Mustard Gas, in Ireland, M W The Medical Department of the United States Army in the World War Medical Aspects of Gas Warfare, Washington, D C, Government Printing Office, vol 14, p 512

5 Gilchrist, H L, and Matz, P B The Residual Effects of Warfare Gases I Chlorine, II Mustard, War Department, Chemical Warfare Service, Washington, D C, Government Printing Office, 1933

6 Roseman, E, and Aring, C D Infectious Polyneuritis, Medicine **20** 463, 1941 Guillain, G Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch Neurol & Psychiat **36** 975 (Nov) 1936 Gilpin, S F, Moersch, F P, and Kernohan, J W Polyneuritis, ibid **35** 937 (May) 1936

7 De Sanctis, A G, and Green, M Acute Infectious Polyneuritis, J A M A **118** 1445 (April 25) 1942

8 Forster, F M, Brown M, and Merritt, H H Polyneuritis with Facial Diplegia, New England J Med **215** 51, 1941

9 Garvey, P H, Jones, N, and Warren, S L Polyradiculoneuritis (Guillain-Barré Syndrome) Following Use of Sulfanilamide and Fever Therapy, J A M A **115** 1955 (Dec 7) 1940

10 Kennedy, F Infectious Neuronitis, Arch Neurol & Psychiat **2** 621 (Dec) 1919

11 Strauss, I, and Rabiner, A M Myeloradiculitis, Arch Neurol & Psychiat **23** 240 (Feb) 1930

12 Aring, C D, and Sabin, A B Fatal Infectious Polyneuritis in Childhood, Arch Neurol & Psychiat. **47** 938 (June) 1942 Honeyman, W M Pathological Study of a Group of Cases Sometimes Referred to as

(Footnote continued on next page)

tionship to preceding infection of the upper respiratory tract,[11] hyperthermia[9] and infection of the gastrointestinal tract[13] has been noted

The onset of the Guillain-Barré syndrome after mustard gas poisoning or exposure may theoretically follow as a consequence of the local effects of mustard gas on the upper respiratory tract,[14] the gastrointestinal tract,[2] the skin[2] or the central nervous system[2], in the preceding circumstances, "activation" of a virus present in the locally affected tissue may have occurred as a result of the local changes induced by this poison or its breakdown products The activation may represent an actual increase in potency of the virus, a decrease in local powers of resistance or a combination of the two factors

REPORT OF A CASE

The patient, a "toxic gas handler," served as an enlisted man in the Chemical Warfare Service in India On July 1, 1944 he was accidentally exposed to mustard gas, which was emanating from a decontamination pit explosion 15 feet (4 5 meters) away The patient immediately recognized the smell of mustard gas and removed his clothes, which were subsequently washed and laundered He was not aware of lacrimation, coughing or sneezing immediately after the exposure, and he considered that in general he had suffered no ill effects On July 5 he again wore the trousers which had been contaminated and continued to wear them for three days By July 10 or 12 severe erythema, blistering and ulceration of both legs and thighs were apparent Admission to a station hospital followed, and there, under local treatment, the ulcerated areas became relatively clean, so that on August 18 skin grafts were applied to these areas, with the patient under spinal anesthesia Casts were applied from just above the knees down to the feet after operation On August 24 the patient was allowed out of bed, but when he attempted to walk he found it difficult to support himself on his legs For the next month the patient contented himself with sitting up in a chair and walking very short distances with the aid of a cane Neurologic examination, on September 24, was reported to show absence of deep reflexes, generalized weakness of the arms and legs and ataxia in performance of the finger to nose test bilaterally The cerebrospinal fluid at this time showed 6 lymphocytes per cubic millimeter and 114 mg of total protein per hundred cubic centimeters Two days later neurologic examination showed impairment of the sense of touch in both lower extremities, loss of appreciation of vibration and position in both knees and feet and marked ataxia in the finger to nose and heel to knee tests Repeated examinations of the cerebrospinal fluid on October 5 showed 1 polymorphonuclear cell per cubic millimeter and 156 mg of total protein per hundred cubic centimeters On October 13 clinical progression of the disease was evidenced by the greater weakness in the lower limbs, complete lack of position sense, absence of cremasteric reflexes, weak abdominal reflexes and absence of deep reflexes On October 14 the cerebrospinal fluid showed 1 polymorphonuclear cell and 1 lymphocyte per cubic millimeter and 281 mg of total protein per hundred cubic centimeters The patient now complained of stiffness and aching of the arms, forearms and hands, and he found it difficult to button his clothes On November 6 he was admitted to this hospital Neurologic examination revealed moderate atrophy of the musculature of the hands and both lower extremities, absence of deep reflexes and a mild to moderate degree of weakness in the extensors and abductors of both shoulders, the abductors of the left thigh, the dorsiflexors of both feet and the extensors of both wrists The patient could walk only a few steps, and this with the aid of two canes A complete blood count and urinalyses revealed normal constituents, and the results of examinations of stools for amebas and parasites and repeated nasopharyngeal cultures for diphtheria bacilli were negative The Schick test gave a negative reaction The roentgenogram of the chest, the electrocardiogram and the electroencephalogram were normal On November 11 the cerebrospinal fluid was under a pressure of 140 mm of water and showed 14 lymphocytes per cubic millimeter and 119 mg of total protein per hundred cubic centimeters, the Wassermann reaction was negative, and the colloidal gold curve was 0001111110 The patient was placed on a high calory, high vitamin diet and received intensive physical therapy in the form of massage, heat and muscle reeducation Within six weeks he had completely regained his strength On December 22 the cerebrospinal fluid was under a pressure of 185 mm of water, and examination showed 10 lymphocytes per cubic millimeter, 48 mg of total protein per hundred cubic centimeters and a colloidal gold curve of 0122221000 The patient was discharged to duty on Jan 13, 1945, at which time he had gained 20 pounds (9 1 Kg) in weight and was neurologically normal except for the continued absence of deep reflexes

SUMMARY

A case of the Guillain-Barre syndrome, with onset after exposure to mustard gas, is reported The activation of the disease by changes induced in the skin, the respiratory tract, the gastrointestinal tract or the central nervous system is considered as a probable mechanism of action

Polyneuritis, Bull Neurol Inst New York **6** 519, 1937 Sabin, A B, and Aring, C D Visceral Lesions in Infectious Polyneuritis, Am J Path **17** 469, 1941

13 Chusid, J G, and Marquardt, G H Acute Infectious Polyneuritis (Guillain-Barre Type), Ann Int Med, to be published

14 Winternitz[3] Gilchrist and Matz[5]

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC

At the annual meeting of the American Board of Psychiatry and Neurology the following officers were elected president, Dr John C Whitehorn, vice president, Dr Percival Bailey, secretary-treasurer, Capt Francis J Braceland

It was voted to amend the by-laws so as to discontinue certification on record as of Jan 1, 1947

The next examination will be held before the meeting of the American Psychiatric Association in Chicago on May 24 and 25, 1946, and before the meeting of the American Neurological Association in San Francisco, June 26, 1946, provided at least 40 candidates appear The list of diplomates certified in December 1945 follows

Neurology and Psychiatry—By Examination Capt Sidney Berman, M C, A U S (formerly Detroit), Major Winston I Breslin, R C A M C (formerly Chicago), Willard C Brinegar, Concord, N H, Alice Boole Campbell, New York, Arthur Attilio Clinco, Brooklyn, Lieut Joseph L Cummings (MC), U S N R (formerly Poughkeepsie, N Y), Charles Fisher, Ellis Island, N Y, Major Herbert S Gaskill, M C, A U S (formerly Philadelphia), Capt Martin Jerome Gerson, M C, A U S (formerly Howard, R I), Paul H Hoch, New York, Samuel P Hunt, Oakland, Calif, Capt Max Edwards Johnson, M C, A U S (formerly Washington, D C), Charles Joseph Katz, Elgin, Ill, Sidney Levin, Boston, Wilmot S Littlejohn, Birmingham, Ala, Hans Lowenbach, Durham, N C, Bruce R Merrill, Bronxville, N Y, Capt Herbert C Modlin, M C, A U S (formerly Boston), Major Benedict Nagler, M C, A U S (formerly Newark, N J), Harold H Noran, Minneapolis, Abe Pinsky, Brooklyn, Leon Roizin, New York, Joseph E Rubinstein, New York, Capt Leon Marcus Simms, M C, A U S (formerly Brooklyn), Capt Charles O Sturdevant, M C, A U S (formerly Portland, Ore), George N Thompson, Los Angeles, John Baer Train, New York, Lieut Walter Irvin Tucker (MC), U S N R (formerly Belmont, Mass), Montague Ullman, Brooklyn, George D Weickhardt, Washington, D C, Capt Frederick G Woodson, M C, A U S (formerly Charlottesville, Va)

Neurology and Psychiatry—On Record Ralph Edward Davis, Boise, Idaho, Robert L Dixon, Caro, Mich, Ernst Lewy, Topeka, Kan

Psychiatry—By Examination Alan B Adam, M C, A U S (formerly Cleveland), Lieut Col Freeman Hornbrook Adams, M C, A U S (formerly Washta, Iowa), Capt Morris Harold Adler, O R D, A U S (formerly Flushing, N Y), Abraham H Ascher, Brooklyn, Alfred K Baur, Washington, D C, Ralph Brancale, Attica, N Y, *Thomas C Carey, Hartford, Conn, Comdr Raymond Stanley Clark, U S N T C (formerly Los Angeles), Robert B Clarke, Ann Arbor, Mich, Louis Allan Cohen, Little Rock, Ark, Sidney Drobnes, Norwich, Conn, Capt Herbert A Duncan, M C, A U S (formerly Baltimore), Capt Marcus Brown Emmons, M C, A U S (formerly Iowa City), Abraham A Fabian, New York, Dora Fishback, Chicago, Fritz Adolf Freyhan, Farnhurst, Del, Douglas Goldman, Cincinnati, Lieut (jg) Sidney Lewis Green (MC), U S N R (formerly New York), Harold A Greenberg, Chicago, Milton Greenblatt, Boston, Major Bernard L Greene, M C, A U S (formerly Chicago), Werner Hochstetter, New York, Roger William Howell, Ann Arbor, Mich, Paul E Huston, Iowa City, Ralph B Jacoby, Brentwood, N Y, Joseph G Kepecs, Chicago, Edward Fox Kerman, Sykesville, Md, Comdr Henry Ambrose Kildee, M C-V(S), U S N R (formerly Roanoke, Va), Major Paul Kramer, M C, A U S (formerly Chicago), Samuel R Lehrman, New York, Lieut Comdr William Taylor Lhamon (MC), U S N R (formerly New York), Samuel Liebman, Winnetka, Ill, Harry B Luke, West Brentwood, N Y, Capt S Albert Molle, M C, A U S (formerly Toledo, Ohio), Claude Linwood Neale, Richmond, Va, Max Needleman, New York, Douglas Noble, Washington, D C, Samuel Novey, Baltimore, Lieut Lucy D Ozarin, U S N R (formerly Helmuth, N Y), Ferdinand R Pitrelli, Central Islip, N Y, George E Poucher, M C, A U S (formerly Chicago), John J Prusmack, M C, A U S (formerly Clarinda, Iowa), Major Leon L Rackow, M C, A U S (formerly Roanoke, Va), Angelo J Raffaele, Willard, N Y, *Capt Harold Ribner, M C, A U S (formerly Bridgeport, Conn), Capt George A Rickles, M C, A U S (formerly Seattle), Herman Rickless, Westborough, Mass, Capt Hector J Ritey, M C, A U S (formerly North College Hill, Ohio), Major William Laray Roach, Med Br, W D P C, Martin H Robinson, Philadelphia, Lieut Comdr Alan Roos (MC), U S N R (formerly Ridgefield, Conn), Capt Lawrence J Roose, M C, A U S (formerly Orangeburg, N Y), William Byron Rossman, Ellettsville, Ind, Capt William P Shelton, M C, A U S (formerly Kansas City, Mo), Capt Samuel Silverman, M C, A U S (formerly New York), Capt Werner Simon, M C, A U S (formerly Palo Alto, Calif), Alice Slater, Elmhurst, N Y, George K Swartz, Norristown, Pa, Comdr J Peter Thornton, M C-V(S), U S N R (formerly Boston), John H Trevaskis, New York, Major Philip Sigmund Wagner, M C, A U S (formerly Fresno, Calif), *Albert L Wanner, Wheeling, W Va, Edward K Wilk, Middletown, Conn, Katherine W Wright, Chicago, *Howard Zeitlin, Chicago, Marion Estelle Zonnis, Petersburg, Va

Psychiatry—On Record Harry Shook Blossom, Patton Calif, Chester Lee Carlisle, Palo Alto, Calif, Jewel Fay, Berkeley, Calif, Ina Moore Freshour, Norwalk, Calif, Lieut Col Charles W Grady, M C, A U S (formerly Palo Alto, Calif), Earle Vincent Gray, Helmuth, N Y, Wirt Clarence Groom, Poughkeepsie, N Y, George W Henry, New York, Richard T O'Neil, Northampton, Mass, Love Elree Pennington, Milledgeville, Ga, Veronica Murphy Pennington, Milledgeville, Ga, Robert Clarence Robertson, Dayton, Ohio, George Wilse Robinson, Kansas City, Mo, Major John Walter Wills, M C, A U S (formerly Palo Alto, Calif)

Neurology—By Examination *Matthew Brody, Brooklyn, *Gerhard Chrzanowski, West Brentwood, N Y, *Lieut Col Ralph T Collins, M R C (formerly Mamaroneck, N Y), Lieut Comdr Stanley M Dillenberg, M C-V(S), U S N R (formerly New York), *Franklin Smith Dubois, New Canaan, Conn, Arnold Phineas Friedman, New York, *Nicholas G Frignito, Philadelphia, *Joseph Julian Gitt, St Louis, *Major Arthur J Lapovsky, M C, A U S (formerly Brooklyn), *Alan A Lieberman, Elgin, Ill, Capt Samuel Clements Little, M C, A U S (formerly Ann Arbor, Mich), Herman Arnold Meyersburg, U S N Training and Distributing Center (formerly Charlottesville, Va), *Major Irvin I Schatz, M C, A U S (formerly Pueblo, Colo)

Neurology—On Record *Lieut Col Harold E Foster, M C, A U S (formerly Northport, N Y)

*The asterisk indicates complimentary certification

Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Anatomy and Physiology

AN EXPERIMENTAL ANALYSIS OF THE INFERIOR MESENTERIC PLEXUS ALBERT J HARRIS, J Comp Neurol **79** 1 (Aug) 1943

Harris made 3 series of experiments on the different nerves connected with the inferior mesenteric plexus in the cat in order to determine the origin of the fibers connected with the plexus and their number After cutting the nerves, twenty-five to twenty-nine days were allowed for degeneration of the divided nerve fibers before the animals were killed Two specimens were taken from each of three nerves, viz, the inferior mesenteric, the hypogastric and the intermesenteric The intermesenteric nerves run between the aortic plexus and the inferior mesenteric ganglia and are composed of the fibers of the lumbar splanchnic nerves and fibers which come from higher levels in the aortic plexus Half the samples were fixed in osmium tetroxide, and the other half were prepared by the Bodian protargol (strong protein silver) method to show both myelinated and unmyelinated fibers The intact fibers were counted under an oil immersion lens Twenty anatomic dissections were also made

Harris found that about 4,000 preganglionic sympathetic fibers entered the inferior mesenteric ganglia Of these, about 1,000 extended into the pelvis via the hypogastric nerves On the average, 3,250 postganglionic fibers entered the ganglia from the sympathetic trunk and 6,500 postganglionic fibers originated in the inferior mesenteric ganglia The visceral afferent fibers numbered approximately 5,000 on the distal side of the ganglia and 2,500 on the proximal side This difference is explained on the assumption that the afferent fibers, on the average, each give rise to one collateral

ADDISON, Philadelphia

AN EXPERIMENTAL STUDY OF THE DEVELOPMENT OF THE MEDIAL LONGITUDINAL FASCICULUS IN THE CHICK RUTH RHINES, J Comp Neurol **79** 107 (Aug) 1943

Rhines attempted an analysis of the various components of the medial longitudinal fasciculus as development proceeded in early chick embryos At the end of three hours' incubation she examined the brains of 18 chick embryos on which she had not operated and operated on 37 others of the same age The operation consisted in removing variable amounts of the rostral end of the brain tube by means of a hair loop and allowing the embryos to continue incubation until 4 to 6 days of age In 2 chick embryos a gap was made in the midbrain, and in 3 embryos the brain was divided at the level of the otocyst The embryos were prepared by a pyridine silver method to show the nerve fibers After four days of incubation fibers from the interstitial nucleus in the diencephalon descended homolaterally in the upper portion of the midbrain and overlapped with ascending fibers from nuclei situated near the sulcus limitans in the trigeminal region Vestibular fibers began to contribute to the caudal end of the medial longitudinal fasciculus at 3 days of age Descending vestibular fibers reached the upper vagus region Spontaneous motility, like that of intact embryos, was seen at 5 days in all types of embryos which had been operated on Rhines concludes that in the chick early spontaneous movements are not dependent on centers rostral to the mesencephalon

ADDISON, Philadelphia

THE ASCENDING AUDITORY PATHWAY IN THE BRAIN STEM OF THE MONKEY W T BARNES, H W MAGOUN and S W RANSON, J Comp Neurol **79** 129 (Aug) 1943

The authors studied the brains of 10 monkeys in which different parts of the auditory system had been destroyed The lesions were made in the cochlear nuclei of 4 animals, in the superior olivary complex of 2, in the nucleus of the lateral lemniscus of 2 and in the inferior colliculus of the midbrain of 2 The brains were removed two weeks after operation, and serial sections were prepared by the Marchi method The sections showed three distinct transverse striae—dorsal, intermediate, and ventral, or trapezoid body The dorsal stria took origin in the dorsal cochlear nucleus and traversed the reticular formation ventral to the medial longitudinal fasciculus, thus it did not have a superficial position in the floor of the fourth ventricle, as described for man The intermediate and ventral striae began in the ventral cochlear nucleus A large number of fibers in all three striae synapsed in the contralateral superior olivary complex with neurons which ascended in the lateral lemniscus Many other fibers of all three striae converged after crossing, turned at right angles in a rostral direction and ascended in the lateral lemniscus A considerable number of fibers from the cochlear nucleus of one side synapsed in the homolateral superior olivary complex and began a homolateral acoustic pathway The succeeding relay stations, where synapses of part of the fibers occurred, were the nucleus of the lateral lemniscus, the nucleus of the inferior colliculus and the medial geniculate body The end station in each hemisphere was in the anterior transverse temporal gyrus of the cerebral cortex

ADDISON, Philadelphia

POLYDACTYLY AND ANTERIOR HORN CELLS IN FOWL LISBETH BAUMANN and WALTER LANDAUER, J Comp Neurol **79** 153 (Aug) 1943

Baumann and Landauer made counts of the motor nerve cells in the lumbosacral region of 8 adult fowls which had five toes on one foot and four toes on the other For comparison, they studied 2 fowls with five toes on each foot, and 3 fowls with the normal number, four, on each foot In the fowl the motor cells of the lumbosacral region may be grouped in six columns, and of these the cells of the dorsolateral and retrodorsolateral columns furnish most of the innervation of the leg and foot The cell counts in these columns showed always a greater number of motor cells on the side with the extra toe The authors consider that the asymmetry in the numbers of motor neurons occurs in consequence of hereditary asymmetries in peripheral structures

ADDISON, Philadelphia

Anatomy and Embryology

THE CONVOLUTED VESSELS OF BRAIN AND SPINAL CORD RUDOLPH ALTSCHUL, J Neuropath & Exper Neurol **3** 386 (Oct) 1944

Altschul reports his observations on the convoluted vessels of the brain and spinal cord The material, which consisted of normal and pathologic brains and spinal cords, was studied by several methods, but for the most part the modified Van Gieson stain for thick sections and Mallory's connective tissue stain for thin sections were utilized

In spite of considerable variability in the regional distribution of convoluted vessels, Altschul reports that they are frequently found in the premotor area but are rare in the precentral gyrus They occur more frequently in the gray-white zone of the insula than in any other part of the central nervous system They are relatively frequent in the parietal lobe except in the postcentral gyrus, where they are rare They are not common in the temporal and occipital lobes and are absent in the cornu ammonis and the cerebellar cortex They are present in the white substance surrounding the dentate nucleus They are met with rather frequently at the periphery of the thalamus and lenticular nucleus but are rarely found around the caudate nucleus Relatively many convoluted vessels are found between the white substance of the basis pedunculi and the adjacent substantia nigra, but here their course is less curled than in other areas They are rarely found in the pons, medulla and inferior olive

In the spinal cord the convoluted vessels occur in the border zone between the lateral white columns and the gray substance and also in the outer zone of the posterior horn No statement can be made about a segmental distribution

In some instances a difference in the rate of growth of the gray and the white matter may explain the form of the convoluted vessels In others the size of the blood vessels probably influences the occurrence of the tortuosities, because, with the possible exception of some vessels of the spinal cord, the convoluted portion is always found in the arterial segment In addition to the factor of size, it is possible that some hitherto unknown peculiarities of the mother vessels may be a determining element

Observations on pathologic material fail to confirm previous observations which indicate that convoluted vessels result from shrinkage of the parenchyma or from the absolute lengthening of the vessel or that they represent parts of newly formed vessels

In 6 cases of epilepsy convoluted vessels were present in the gray substance proper and were more numerous than under normal conditions In 1 case they were present in the cornu ammonis They were not found in 3 other cases of epilepsy, but the small arteries of the pia were convoluted In 2 cases of Huntington's chorea the convoluted vessels were increased in number and were situated farther inward than in normal brains However, in 1 case no abnormalities of the convoluted vessels were present

At this time it is not possible to make a statement as to whether or not there is a causal connection between the convoluted vessels and the clinical symptoms

GUTTMAN, Philadelphia

AN INTRACELLULAR BODY IN THE HUMAN CHOROID PLEXUS EPENDYMA AND ITS ANALOG IN THE RETINAL PIGMENT LAYER CELLS OF THE ALBINO RAT A E TAFT, J Neuropath & Exper Neurol **3** 416 (Oct) 1944

Taft describes an intracellular body which can be seen in the ependymal cells of the choroid plexus of man and animals In appearance it is similar to a body present in the (nonpigmented) pigment cell layer of the albino rabbit eye In the ependymal cells of the choroid plexus in the Negro, the body itself contains dark brown to black granules, similar in appearance to those seen in the normally pigmented retinal cell layer of the eye

The cells in these two areas are alike morphologically and present a similar contrast to the nerve cells which lie adjacent to them, the ventricular wall of the brain, and the layer of rods and cones of the eye They are also similar in their embryologic development

GUTTMAN, Philadelphia

Physiology and Biochemistry

MECHANISMS OF OCULAR MOVEMENT IN MAN INFLUENCE OF THE VESTIBULAR APPARATUS H B PERLMAN and T J CASE, Arch Otolaryng **40** 457 (Dec) 1944

The objective of every movement of the eyes is clear macular vision This is attained by keeping the foveas opposite the area of interest for a minimal time, about one-fifth second The most restful or most easily maintained position for the eyes is the central one In going from one point of fixation to another the eyes always move rapidly Movement of the eyes may be (1) voluntary (frontal cortex), (2) reflex optic (occipital cortex activated by a retinal image) or (3) reflex vestibular (activated by end organs in the labyrinth) In order that all the demands for movement of the eyes may be met, all three mechanisms must be working normally Some movements result from a temporary preponderance of the activity of a single center Other movements represent the associated hyperactivity of several centers

In the motor area of each frontal lobe there is a center for movement of the eyes which enables one to move the eyes away from the center voluntarily The ocular muscles are thus voluntarily contracted and overcome the tonic muscle reflexes operating to keep the eyes in the resting midposition The cortical centers enable the subject not only to move his eyes away from center and keep them there but to make this movement rapidly from one position to another This can be done under closed lids, that is, without retinal images, or it may be aided by vision—when fixation on a point in one area is rapidly followed by fixation on a point in the new area after the eyes have been moved With or without retinal images, this voluntary movement is carried out very rapidly, in about one-twentieth second

Motor fibers that enable the eyes to turn toward an object in the periphery of the visual field, that control fusion, convergence and other activities, originate in the occipital, or visual, cortex This center is also the source of motor fibers for the ocular muscles concerned with ability of the eyes to follow a moving object This is not a conscious rapid voluntary movement, like that initiated from the frontal lobe, but a reflex movement, the speed of which is largely controlled by the speed of the moving object and requires retinal stimuli to

sustain it The retinal images need not be clear This neural mechanism that makes the eyes follow a moving object can operate even when the occipital cortex is destroyed, presumably through reflex activity at a subcortical level—initiated by moving retinal images An example of normal cortical function moving the eyes through a small area rapidly and accurately from one point of fixation to another is seen in reading Here the head may remain motionless, the eyes being moved rapidly to four or six successive points of fixation to obtain retinal images for all the words in one line, then the eyes are moved suddenly and accurately all the way back to the beginning of the next line Ocular movements may be initiated directly from the frontal cortex or reflexly from the occipital cortex by retinal stimuli The cerebellum cannot initiate ocular movements but is concerned with the tonus of the extraocular muscles

The vestibular apparatus is not important for normal movement of the eyes in man Most normal demands for movement of the eyes can be met by a subject with no vestibular function Stimulation of the vestibular end organs can, however, initiate movement of the eyes The fundamental ocular movement resulting from stimulation of the vestibular end organ is slow conjugate deviation away from center, it depends on bending of the hair cells by motion of the cupular substance in which they are embedded The normal physiologic stimuli for this end organ are movements of acceleration and deceleration It is a reflex phenomenon, which has a short latent period The ability to see clearly while moving the head (to move the eye accurately in order to keep it on a point of fixation while the head moves) is perhaps aided by the induced vestibular ocular reflex arising from accurately balanced vestibular mechanisms

In the presence of spontaneous vestibular nystagmus, more pronounced movements of the eyes are observed when the subject deviates his eyes toward the side of the quick component than when he turns them in the direction of the slow component This may be explained on the basis of superimposition of vestibular impulses (slow pull) on the tonic impulses tending to move the eye toward center This results in the cortical stimuli, which operate to maintain deviation, becoming more rapidly inadequate and leads to frequent and more quick movements When such a person turns his eyes in the direction of the slow component, the eyes can be better maintained in the deviated position, since the vestibular stimulus operating to move the eyes slowly in that direction is now working against the tonic muscle stimuli operating to move the eyes slowly back toward center Therefore the cortical centers operating to maintain the eyes in the deviated position function more adequately, and the globes are more quietly maintained in that deviated position If the final common pathways (posterior longitudinal bundle and others) for all ocular movements are affected in the pons, none of the mechanisms for ocular movement may work because of paralysis of the ocular muscles This may be a unilateral or a bilateral involvement, such as occurs with pressure on or disease of the pons If unilateral, the unopposed pull of the ocular muscles on the nonparalyzed side may keep the globe deviated away from center and away from the side of the lesion and prevent any kind of movement (voluntary, optokinetic, vestibular) of the globe beyond center toward the side of the lesion A peripheral lesion of the nerve for the ocular muscle may lead to similar results

RYAN, M C, A U S

FURTHER OBSERVATIONS ON THE PRESENCE OF POLIOMYELITIS VIRUS IN THE HUMAN ORO-PHARYNX HOWARD A HOWE, DAVID BODIAN and HERBERT A WENNER, Bull Johns Hopkins Hosp **76** 19 (Jan) 1945

Howe, Bodian and Wenner report observations on 36 patients who had poliomyelitis Intracerebral inoculation of rhesus monkeys with inoculum from the oropharynx was employed The criterion for successful isolation of virus was the production of flaccid paralysis with typical lesions in the spinal cord of the experimental animals, or the production of indubitable lesions alone (1 case)

Virus was recovered from the oropharynx of 10 animals, or 28 per cent Virus was present in 43 per cent of a series of 23 patients from whom swab specimens were taken during the first three days of the illness In none of the series of 13 cases in which specimens were obtained after the third day of illness was the virus isolated

GUTTMAN, Philadelphia

STUDIES ON SHOCK THERAPY JUAN NEGRIN JR J Nerv & Ment Dis **101** 15 (Jan) 1945

Negrin studied the variations produced in cerebrospinal fluid pressure by taking the pressures immediately before and from ten to thirty minutes after electric shock therapy in 3 patients There was a definite decrease in pressure in 5 of 8 determinations following grand mal convulsions, while no appreciable change was recorded after 3 petit mal episodes The author suggests that the observations indicate a possible method of studying the correlation of cerebrospinal fluid pressures with venous and arterial pressures

CHODOFF, Langley Field, Va

CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDIES THE ELECTROENCEPHALOGRAM IN PSYCHONEUROTICS HANS STRAUSS, J Nerv & Ment Dis **101** 19 (Jan) 1945

Strauss studied the electroencephalograms of 100 psychoneurotic patients and compared the patterns obtained with those of 100 control persons Each record was analyzed for the alpha index, the duration of the runs of alpha activity and the general pattern of electrical activity In general, the psychoneurotic patients yielded records with less predominance, less continuity and a less amount of alpha activity than were found in the records of the control group Patients with chronic anxiety and impairment of mental performance were especially apt to have tracings with a small amount and poor quality of alpha activity With hyperventilation some psychoneurotic patients showed a decrease in the amount and continuity of alpha activity, an observation contrary to the usual increase of or absence of change in this activity

The fact that alpha activity is decreased in tense psychoneurotic persons can be correlated inversely with the general rule that the amount of alpha waves is increased under conditions of mental and emotional relaxation Thus, the occurrence of a record showing good quality and continuity of alpha activity in a subject with an apparently severe and chronic psychoneurosis may throw doubt on the depth of the patient's difficulties, conversely, a record showing poor alpha activity in a person suffering from what is apparently only a situational reaction should raise the suspicion of a more

deep-seated emotional disturbance The improvement in alpha activity seen with hyperventilation in some of the cases indicates that the business of hyperventilation is sufficiently absorbing to push into the background ideas associated with emotional tension No delta activity with the patient at rest was seen in any of the psychoneurotic subjects studied, and the author feels that delta activity in a patient with alleged psychoneurosis should raise the suspicion of an underlying focal or metabolic disorder

CHODOFF, Langley Field, Va

THE CEREBROSPINAL FLUID AFTER ELECTRIC CONVULSIVE THERAPY JAMES F MADDUX and C KNIGHT ALDRICH, J Nerv & Ment Dis **101** 330 (April) 1945

Maddux and Aldrich find that there has been little in the literature with regard to changes in the cerebrospinal fluid following electric shock therapy The authors studied the spinal fluids of 10 young male patients with schizophrenia The pressure and dynamics of the cerebrospinal fluid were within normal limits on all examinations The benzidine and Pandy tests gave negative results, and the colloidal gold curve was within normal limits in all cases The cell count, the total protein content and the levels of sugar in the blood and spinal fluid were likewise always within the normal range There were no significant differences in the results of examinations made before and after one to ten convulsive treatments

CHODOFF, Langley Field, Va

SYNTHESIS OF ACETYLCHOLINE BY TISSUE OF THE CENTRAL NERVOUS SYSTEM W FELDBERG, J Physiol **103** 367, 1945

Feldberg has extended previous investigations in which it was shown that acetylcholine is synthesized by slices of brain tissue It was found that dried and powdered brain substances when suspended in physostigmine-saline solution also synthesized acetylcholine The synthesis was accelerated by the presence of ether and was depressed, but not consistently abolished, by procedures which interfere with the utilization of oxygen

The most satisfactory synthesis occurred in suspensions of brain powder in the presence of ether at room temperature At body temperature the synthesis was accelerated at first but did not continue as long as at room temperature

Glucose, which accelerates the synthesis by brain slices in appropriate concentration, had no such effect on the synthesis by brain powder Higher concentrations of glucose inhibit the synthesis in brain slices The normal blood sugar concentration is inhibitory Calcium ions inhibited the synthesis in both preparations Potassium chloride increased the synthesis of acetylcholine by respiring tissue slices and in suspensions of brain powder The effect in tissue slices was prevented by ether

THOMAS, Philadelphia

EXCITABILITY CHANGES AT THE NEURO-MUSCULAR JUNCTION DURING TETANY STEPHEN W KUFFLER, J Physiol **103** 403, 1945

Kuffler produced tetany in cats by removing the parathyroid glands and in frogs either by removing the parathyroid glands or by injection of 0 2 to 0 4 cc of a 2 5 per cent solution of sodium citrate into the dorsal lymph sac The symptoms were the same regardless of the method used Particular interest attaches to the results with denervated muscles, which were similar in the two species of animals The symptoms consisted of fasciculation (synchronous contractions of groups of muscle fibers) and fibrillation (asynchronous twitching of individual muscle fibers) The latter was more frequent and occurred in all preparations Fasciculation was present in the denervated muscles only during the time required for degeneration of the cut nerve and was attributed to random nerve impulses in the degenerating fibers

An electric record from the nerve-free end of the fibrillating sartorius muscle showed that the contractions originated in the region of the nerve endings

The author mentions, but does not describe, experiments which indicate increasing irritability of central synapses during tetany He concludes that the symptoms of tetany result from lowering of the threshold at the synapses and end plates

THOMAS, Philadelphia

FACILITATION, INHIBITION AND DEPRESSION AT THE ARTIFICIAL SYNAPSE FORMED BY THE CUT END OF A MAMMALIAN NERVE RAGNAR GRANIT and C R SKOGLUND, J Physiol **103** 435, 1945

This work extends a previous study in which it was shown that nerve impulses transmitted over efferent fibers in a mixed nerve are relayed to afferent fibers in the same nerve at a region of injury caused by crushing or cutting the nerve The cut end of the nerve behaves like an artificial synapse This artificial synapse has many properties characteristic of the natural synapse, for example, synaptic delay and sensitivity to anoxia, fatigue and anesthetics The author states that in order to behave as an artificial synapse the cut end of the nerve "must be in very good condition" The changes in irritability of the artificial synapse following a conditioning stimulus were studied There is a refractory period followed by a period of hyperexcitability and in some preparations a series of rhythmic changes in irritability lasting up to twenty microseconds The artificial synapse manifests dynamic polarity to the extent that transmission is generally better from motor to sensory fibers than in the opposite direction They also exhibit the phenomena of facilitation and inhibition

THOMAS, Philadelphia

Diseases of the Brain

HISTAMINE CEPHALALGIA AND MIGRAINE LOUIS E LIEDER, Ann Int Med **20** 752 (May) 1944

Lieder studied 71 consecutive patients with headache, devoting special attention to the question of allergy Analysis of the cases showed that 4 patients had histamine cephalalgia, 52 had typical migraine and the remaining 15 had other types of headache, such as so-called hypertensive cephalalgia and anxiety states Twenty-eight (54 per cent) of the 52 patients with migraine had food allergy Twenty-three (44 per cent) of the migrainous patients had allergies such as so-called hay fever, urticaria and asthma A family history of some allergic manifestation or of migraine was obtained from 40 patients (77 per cent) The author concludes that "hypersensitivity plays a major role in causing migraine"

Desensitization with histamine was found to be of value in the successful treatment of patients with histamine cephalalgia Ergotamine tartrate was recom-

mended for the treatment of migraine, and the use of neostigmine bromide, prophylactically and therapeutically, and inhalation of oxygen were mentioned

Lieder stresses the fact that the elimination of offending allergens is of utmost importance in the prevention of migraine

GUTTMAN, Philadelphia

FOSTER KENNEDY SYNDROME WITH FUSIFORM ANEURYSM OF INTERNAL CAROTID ARTERIES I S TASSMAN, Arch Ophth **32** 125 (Aug) 1944

Tassman reports the Foster Kennedy syndrome in a case of bilateral fusiform aneurysm of the carotid artery The patient's only complaints were pain over the right eye and loss of vision in the left eye The left eye was nearly blind, so that no field was present, and in the right eye there were slight constriction and enlargement of the blindspot Operation revealed the following "The left nerve was of normal size and appearance It was entirely free and not compressed by any visible lesion Just beneath it was a fusiform aneurysm of the internal carotid artery, which after emerging from the base of the skull formed a complete loop into the region of the sella turcica and then passed backward to its normal location to progress laterally to the middle cerebral artery It appeared as though the artery was bound to the base of the skull by the ophthalmic artery On the right side there was a similar fusiform aneurysm, with a mass of tiny veins on it, just beneath the optic nerve This pressed the optic nerve backward tightly against the posterior edge of the optic foramen It was impossible to do anything surgically with the lesion It is believed that ocular difficulty on the left side was caused by sclerosis of the ophthalmic artery, because obviously there was not enough pressure against the optic nerve to cause atrophy and blindness The pressure against the optic nerve on the right side was definite enough to cause progressive blindness, although one would think there would be atrophy rather than edema of the disk on that side The pressure, however, may have been just sufficient to cause congestion of the venous blood returning from the orbit"

The paper emphasizes one thing especially—that a number of cases of the Foster Kennedy syndrome with non-neoplastic causes have now been reported

SPAETH, Philadelphia

CHRONIC EXTRADURAL ABSCESS IN CHILDREN JOHN B PRICE, Arch Otolaryng **40** 501 (Dec) 1944

Price reports a series of 7 cases of extradural abscess associated with mental deficiency Six patients were boys ranging from 3 to 13 years of age, the girl was 7 years old Mastoidectomy was performed because of chronically discharging ears, and extradural abscess was found in all 7 cases, being bilateral in 2 cases After discovery and treatment of the extradural infection, the children's behavior showed great improvement

The author believes that the abnormal behavior in the cases reported was the result of pressure from an extradural abscess on the brain He believes that infections surrounding the brain should always be searched for and all chronically discharging ears should be explored and treated when these conditions are present in mentally backward children

RYAN M C, A U S

THE ENDOCRINE GLANDS IN AMAUROTIC FAMILY IDIOCY OTTO MARBURG, J Nerv & Ment Dis **100** 450 (Nov) 1944

Prompted by the finding of normal electrical reactions in the asthenic muscles in cases of amaurotic family idiocy, Marburg sought the cause of the asthenia in the endocrine organs The author studied 3 cases of the disease in children of 1 year 11 months, 3 years and 1½ years in which autopsy was done In each of the 3 cases there was almost complete absence of adrenal medullary substance and complete lack of chromaffin tissue This observation is in keeping with the observations in other cases of Tay-Sachs disease with autopsy On the other hand, the gonadal cells in all 3 cases were prematurely developed, while the interstitial cells of the ovaries and testes were degenerated Relative hyperplasia of the thymus gland was observed in the cases, together with an appearance indicating functional insufficiency There was some increase in the colloid of the thyroid, while the hypophysis, parathyroids and pancreas were intact

The asthenia of amaurotic familial idiocy is thus considered analogous to that seen with Addison's disease and is due to destruction of the adrenal medulla A similar type of endocrine constellation is found in myasthenia gravis, exophthalmic goiter, amyotonia congenita and possibly familial periodic paralysis The asthenia in these conditions is presumably due to disturbances in the acetylcholine mechanism

CHODOFF, Langley Field, Va

THE PSYCHIATRIC SEQUELAE OF POST-MEASLES ENCEPHALITIS EDWARD C SMITH and CARL E TRAPP, J Nerv & Ment Dis **100** 555 (Dec.) 1944

Smith and Trapp report 21 cases of encephalitis following measles studied with regard to the patient's previous history, the neurologic status and the adjustments five and a half years after recovery All the patients were between the ages of 4 and 12 years, and all were white children Encephalitis appeared from one to ten days after the diagnosis of measles had been made Common signs were convulsions, stiff neck, Kernig's sign, coma and paralyses Complete recovery occurred in from six to thirteen days In 8 of the cases personality changes followed the encephalitis, these were pronounced in 5 cases In some cases emotional instability prior to the illness made the degree of damage due to encephalitis difficult to evaluate In all 8 cases some objective neurologic sequelae, such as hypotonia, strabismus, convulsive state, Babinski's sign, hyperreflexia or pupillary abnormalities, were present

CHODOFF, Langley Field, Va

ENCEPHALO-TRIGEMINAL ANGIOMATOSIS JOHN R GREEN, J Neuropath & Exper Neurol **4** 27 (Jan) 1945

Green reports a case of a 3 year old boy who had a "port-wine birthmark" over the right frontal and parietal regions, including the area supplied by the first two divisions of the trigeminal nerve on that side He had frequent and severe left-sided jacksonian seizures, which began after the age of 6 months In addition, there were left hemiparesis, hemiatrophy of the left side of the body and mental retardation An area of nonactivity was localized by electroencephalographic study in the right postparietal region Roentgenograms

of the skull revealed marked asymmetry, the left side being larger than the right Sinuous, double-contoured calcifications were present in the right anterior parietal region Pneumoencephalograms showed marked atrophy of the right cerebral hemisphere and moderate dilatation of the right lateral ventricle Stereoscopic arteriograms revealed increased vascularity and an abnormal tangle of small vessels in the distribution of the middle internal frontal, posterior internal frontal, paracentral and superior parietal branches of the right anterior cerebral artery and of the posterior parietal and central branches of the right middle cerebral artery There were decreased circulation time through the same vessels, incorporation of the areas of calcification into the terminal distribution of the right superior and posterior parietal arteries on the right side and upward deviation of the terminal portion of the right anterior cerebral artery Craniotomy was performed, and a hemangioma in the right parietal region was removed The postoperative course was uneventful, the youngster improved, and the seizures were controlled with phenobarbital

Green concludes that angiomatosis of the scalp, meninges and brain should be suspected when a child who has a "port-wine mark" in the area of the trigeminal nerve presents convulsions, hemiparesis or mental retardation The diagnosis is confirmed by the finding of sinuous, double-contoured calcifications in the roentgenograms of the skull Localization of the pathologic process may be aided by electroencephalographic and pneumoencephalographic studies and, according to Green, should be confirmed by stereoscopic angiograms, especially in cases in which there is no gross calcification

The characteristic calcifications which occur in the upper layers of the cortex probably represent calcareous degeneration of primary angiomas

Green, though not unmindful of the contributions of Sturge, Kalisher, Weber, Krabbe and others, suggests that the classification of such conditions preferably be in accordance with descriptive anatomic and pathologic terms because of the variability of the clinical and pathologic pictures A designation like encephalotrigeminal angiomatosis seems appropriate, rather than a contested combination of proper names

GUTTMAN, Philadelphia

CARCINOMA OF THE THYROID GLAND WITH A SOLITARY METASTASIS TO THE SKULL HOLLIS L ALBRIGHT, New England J Med **230** 573 (May 11) 1944

Albright reports the case of a 52 year old housewife who had a carcinoma of the thyroid with metastatic lesion in the right frontal region of the skull Thyroidectomy was performed, followed by partial craniectomy and removal of the metastatic lesion, which had no obvious penetration through the dura A course of roentgen irradiation was directed to the right temporofrontal region A follow-up examination two and one-half years after these procedures failed to reveal any evidence of neoplastic disease

GUTTMAN, Philadelphia

THE HEALING PROCESS IN WOUNDS OF THE BRAIN A H BAGGENSTOSS, J W KERNOHAN, and J F DRAPIEWSKI, Proc Staff Meet, Mayo Clin **19** 419 (Aug 9) 1944

The studies reported by Baggenstoss, Kernohan and Drapiewski were made at necropsy in 70 selected cases in which ventricular puncture had been made for diagnostic purposes It was found that repair was more vigorous in the cortex than in the white matter Astrocytes were found to play a minor role in the reparative process, and actual participation of these cells in the formation of a scar was not observed in wounds of less than six months' duration When repair takes place, the predominant role is played by mesodermal elements —capillaries, endothelium, fibroblasts and leukocytes Microglia cells appeared to have only a small part in the production of compound granular corpuscles Most of the latter seemed to have their origin in the endothelial cells associated with capillaries, in the adventitial cells of the larger blood vessels and in the mononuclear cells of the circulating blood

ALPERS, Philadelphia

ELECTRIC SHOCK IN THE TREATMENT OF DEMENTIA PARALYTICA M C PETERSEN, Proc Staff Meet, Mayo Clin **20** 107 (April 4) 1945

Petersen reports the results of electrical shock treatment in 34 cases of dementia paralytica The ages of the patients ranged from 28 to 60 years The number of shocks administered varied from 2 to 37 Currents of 500 milliamperes applied for 0 2 second were used routinely, but if no convulsion was induced the current was increased to 650 milliamperes The time of application of the current was increased in a number of instances 0 3 second in 12 cases, 0 5 second in 9 cases, 0 7 second in 4 cases and 1 second in 1 case

Of the 34 patients treated, 20 showed great improvement, 9 only slight change and 5 no improvement at all Four patients showing slight improvement had a relapse, but their condition improved again after a second series of shocks The best results were obtained in patients of the agitated group

ALPERS, Philadelphia

FACTORS IN RECOVERY FROM INJURIES TO THE HEAD JOSEPH FETTERMAN, War Med **5** 232 (April) 1944

Fetterman reviews the many factors which influence the recovery of the patient who has had a head injury The decisive elements in recovery come under four main headings the man who is injured, the type of injury, the treatment used and the milieu of the patient.

1 The man who is injured As a rule the younger the patient the better the prognosis The personality of the patient, including his intelligence, his dynamic energy and his patterns of behavior, is highly important in all considerations of sickness Two features of the personality are decisive forces in the reaction of the soldier to injury his aims and his physiologic reaction to difficulties

2 The type of injury The speed and degree of recovery will depend on the pathologic changes These changes will be influenced by the force of the injury, whether the complication of infection occurs and the site of the damage

3 The treatment used Appropriate treatment will include emergency care during the period of shock, measures to provide the optimum conditions for cerebral function, prevention of infection, symptomatic relief and rehabilitation

4 The milieu The primary responsibility in treatment belongs to medicine, but the secondary influence of the milieu is considerable Encouraging contacts, compensation only for organic defects, training and, especially, the chance to be usefully occupied are important helps toward recovery

PEARSON, Philadelphia

PROLONGED POST-TRAUMATIC AMNESIA ADAMS MCCONNELL, Lancet **1**.273 (Feb 26) 1944

McConnell reports 6 cases of post-traumatic amnesia prolonged for more than four days after injury No signs or symptoms were present other than the amnesia, which the author defines as "loss of retention of memory, incapacity to recall recent events, confusion and confabulation" Since other authors have pointed to the ill effects of long-continued traumatic amnesia, McConnell felt justified in breaking the unwritten law that one operates only when hemorrhage is suspected He made a trephine opening "on each side of the skull, opened the dura" and found subdural fluid in 5 of the 6 cases This fluid was "blood stained" or "yellow" or "clear" Therefore the condition in these cases was not subdural hematoma, although in a postcript he adds such a true case Of the 6 patients, 1 died a week after operation of pneumonia, and the rest, including the patient in whom nothing was found at operation, sooner or later recovered The spinal fluid pressure was never over 135 mm of water in any of the 6 patients

The author suggests that the sequence of events was as follows "Concussion caused a lengthy period of amnesia, during this period a subdural effusion developed, interfered further with cerebral function and so prolonged the existing amnesia" The important practical conclusion is that prolonged post-traumatic amnesia merits subdural exploration

McCARTER, Boston

THE CONSTITUTIONAL FACTOR IN ANESTHETIC CONVULSIONS DENIS WILLIAMS and W H SWEET, Lancet **2** 430 (Sept 30) 1944

Williams and Sweet studied 42 cases of convulsions occurring during anesthesia and took electroencephalographic records in 22 of them one month to two years after the operation at which the convulsion occurred Ether was used in 40 cases, divinyl ether in 1 case and pentothal sodium in another In only 1 case had previous seizures occurred, and in only 1 case was there a family history of convulsions, in 1 case there was migraine, and in 6 of the 22 cases there was a history of "fainting spells" The authors felt that about three fourths of the electroencephalographic tracings were abnormal and that evidence of larval epileptic attacks was seen in one fourth There was nothing to suggest that the discharges were in any way different from those observed in cases of idiopathic epilepsy or that the seizures themselves differed clinically from typical grand mal

The authors conclude that convulsions complicating anesthesia are precipitated by any one of a number of factors at the time of operation in patients with an inborn convulsive tendency identical with the tendency assumed to be present in epileptic persons

McCARTER, Boston

NEUROLOGICAL COMPLICATIONS OF RELAPSING FEVER R B SCOTT, Lancet **2** 436 (Sept 30) 1944

Scott describes 9 cases of relapsing fever with neurologic complications in a series of 41 cases of the disease Complications were most common after the third week, although they developed at any time The cases with neurologic complications fell into three classes those with meningitis, those with focal disease of the nervous system and those with both The cerebrospinal fluid showed a total protein content of from 60 to 160 mg per hundred, cubic centimeters and pleocytosis, with lymphocytes decidedly predominant

Treatment with arsphenamine was not helpful Prognosis was hard to assess Some patients had repeated relapses, but the majority recovered completely There were no deaths

McCARTER, Boston

SPONTANEOUS CEREBRAL HEMORRHAGE SURGICAL TREATMENT ANDRES A VEPPO, Prensa méd argent **31** 1542 (Aug 9) 1944

Veppo discusses the possibility of surgical treatment of intracerebral hemorrhage He reports the case of an 18 year old blacksmith who suddenly began to have contractions of the right side of the face for no evident reason A generalized seizure with upward deviation of the eyes appeared soon afterward The next day he had another episode of twitching on the right side of the body, followed by stupor He was hospitalized and was found to be stuporous, but there were no signs of meningeal irritation There was generalized hyperreflexia, with a bilateral Babinski sign, normal pupillary reactions, a pulse rate of 72 and a blood pressure of 122 systolic and 84 diastolic Two days later flaccid paralysis of the right side of the body was noted, but the hyperreflexia continued to be generalized Lumbar puncture revealed a clear spinal fluid The fundi showed blurring of the nasal and inferior edges of both optic disks with some engorgement of the veins There were numerous red cells in the spinal fluid The Wassermann reactions of the blood and spinal fluid were negative The patient failed to respond to medical treatment, and an operation was performed eleven days after admission Ventriculography showed displacement of the ventricular system toward the right A craniotomy was done, and coagulated blood was removed from the subcortical region after the cortex was incised The patient showed progressive improvement Eleven months later he was well except for slight weakness of the right upper limb Three years after the operation the patient was well, with no recurrence of symptoms The cause of the intracerebral hemorrhage was not determined by clinical examination

SAVITSKY, New York

ACOUSTIC NEURINOMA COMPLETE EXTRACAPSULAR EXTIRPATION, ANASTOMOSIS OF ACCESSORY SPINAL AND FACIAL NERVES GERMÁN HUGO DICKMANN, Rev neurol de Buenos Aires **9** 239 (July-Sept) 1944

Dickmann reports the first case from Argentina in which an acoustic neuroma was extirpated completely by the extracapsular method A good result was obtained in a 33 year old white woman with the technics described by Dandy and Horrax An anastomosis between the facial and the spinal accessory nerve was performed eighteen days after extirpation of the tumor, with excellent results

SAVITSKY, New York

OCULOGYRIC INSTABILITY AS INITIAL SYMPTOM IN MULTIPLE SCLEROSIS V A JENSEN, Nord med (Hospitalstid) **21** 580 (March 24) 1944

Jensen reports that oculogyric instability was established in 70 per cent of 50 patients (23 men, 27 women) with multiple sclerosis It was demonstrable in 12 of the 14 patients with duration of the disorder of a year or less For examination of the circumductive leading movement the patient is requested to keep his head still and to follow attentively with the eyes an object, such as the end of a fountain pen, shown to him and then made to describe steadily a not too large circle about 50 cm in front of his face In patients with multiple sclerosis, even in the initial stage, the circular movement on each side often proceeds in a series of jerks, and an irregular, snappy nystagmus occurs each time the eyes reach one or two definite points in the path of the object The second phenomenon is bilateral and occurs most often in the upper quadrants of the range of vision, but not in the horizontal line or the vertical meridian

J A M A

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

HAROLD G WOLFF, M D, *Chairman of the Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Dec 12, 1944

Nerve Regeneration on Vitamin B-Deficient Diets

DR CHARLES M BERRY (by invitation), MR CHARLES NEUMANN (by invitation) and DR JOSEPH C HINSEY

The tibial, peroneal and saphenous nerves of cats were regenerated normally in the presence of pronounced thiamine deficiency The rates and quality of the regeneration were determined by observing the return of function and reflexes, which showed a longitudinal growth of the fibers of from 4 to 5 mm per day Also, measurements of sweating from the foot pads, records of the action potentials from the excised regenerating nerves and microscopic measurements of the diameter growth of the fibers were made The regenerating nerves had been crushed earlier with a thin, flat-surfaced forceps only after the cats had shown signs of deficiency on either a carp diet or on a tube-fed diet The latter contained casein, sugar, corn oil, salts and supplementary vitamins with the exception of thiamine hydrochloride By injecting small doses of thiamine hydrochloride (20 to 50 micrograms daily), the animals were kept alive as long as one hundred and sixteen days, during which period the nerves were allowed to regenerate

The cats on the carp diet, which was deficient in thiamine and other components of the vitamin B complex, showed rapid development of anorexia, ataxia and postural disturbances due to damage of the central nervous system, and convulsions With the better controlled, tube-fed diet the ataxia and convulsions were extremely mild or absent, even in cats which died after periods of up to one hundred and sixteen days Apparently, damage to the heart produced death in all the cats with thiamine deficiency

The peripheral nerves, which were excised immediately after the cats died of thiamine deficiency, showed normal action potentials, which demonstrated the ability of all the fiber components in the nerves to conduct impulses Likewise, microscopic examination showed no damage to peripheral nerves in the thiamine-deficient cats

DISCUSSION

DR NORMAN JOLLIFFE I enjoyed hearing this paper, and in discussing it I have an opportunity to emphasize the difference between acute and chronic lesions associated with deficiency diseases, particularly thiamine deficiency The acute lesions of thiamine deficiency, whether they are in the pigeon, the dog or the human being, are very similar in that there is no damage to the peripheral nervous system These animals, and man for that matter, will die of an acute metabolic defect before any damage to the peripheral nerves is evident Lack of appreciation of this fact led Meiklejohn (*New England J Med* **223** 265, 1940) to question seriously whether thiamine is the antineuritic vitamin It also caused Williams and his associates (Williams, R D, Mason, N L, Wilder, R M, and Smith, B F Observations on Induced Thiamine [Vitamin B_1] Deficiency in Man, *Arch Int Med* **66** 785 [Oct] 1940), after failing to observe polyneuritis in a group of women maintained on a diet containing about 0 15 mg of thiamine per thousand calories, to suggest that perhaps thiamine is not the antineuritic vitamin It was not until these authors placed their patients on a diet containing a larger amount of thiamine that polyneuritis developed In other words, with a diet very deficient in thiamine the metabolic defect is so prominent as to prevent the development of polyneuritis Dr Berry and his associates recognized these facts in their studies, though in their chronic animals the did not produce a true chronic deficiency For example, in their chronic cats they produced an acute deficiency in about twenty days and then proceeded to give parenterally 20 to 50 micrograms of thiamine hydrochloride, which was sufficient to permit these animals to live forty to one hundred and sixteen days Such a period is probably too short, especially one of less than ninety days, for a cat to show chronic polyneuritis In addition, these animals did not present lesions of the peripheral nerves Such lesions are pathognomonic of chronic thiamine deficiency A good way to tell whether one has produced chronic lesions of the peripheral nerves in animals is to give a dose of thiamine hydrochloride If there is prompt response, one is reasonably sure that there is no degeneration of peripheral nerves If there is no response, anatomic lesions probably are present, and the experimenter will be able to demonstrate them pathologically I suggest to Dr Berry and his coworkers that they place their animals on 20 to 50 micrograms of thiamine hydrochloride from the beginning, allow signs of damage to the peripheral nerves, to develop and then give the animals a large dose of thiamine hydrochloride If the peripheral nerve signs do not respond promptly, the investigators will have suitable animals in which they can study the effect of a chronic deficiency of thiamine on nerve regeneration following injury

DR CHARLES M BERRY Wintrobe, Follis, Humphreys, Stein and Lauritsen (*J Nutrition* **28** 283, 1944) found no damage to the nervous system in swine after eight months of thiamine deficiency with a well controlled diet However, in previous work, Wintrobe and associates (*J Exper Med* **68** 207, 1938) and Kolb and associates (*Trans Am Neurol A* **67** 189, 1941) produced lesions of the peripheral nerves with diets deficient in compounds of the vitamin B complex other than thiamine

DR JOSEPH C HINSEY I shall not argue the point with Dr Jolliffe as to whether we are dealing with an acute, or chronic state Under the conditions of the experiments as we described them, we found the capacity of the nerve to regenerate to be fairly normal It seems fairly important that even in the acute state peripheral nerve tissue has the capacity to grow in a fashion which simulates the normal, as nearly as one can study it in normally fed animals I think that is the point which is of the greatest interest to me in this series of experiments

PSYCHOSOMATIC PROBLEMS

Genetic and Conditioning Factors in Susceptibility to Disease DR GEORGE DRAPER

Since human disease embraces man as well as his environment, inquiry into the human being's nature is an essential task of the physician Every effort should be made to study the patient's genetic structure and to observe the modes of response to the inner and outer conditioning factors which effect modifications of the original protoplasmic plan Three cases are cited as illustrations

The first, a case of sepsis and pneumonitis due to hemolytic Staphylococcus aureus, was presented to show the direct conflict between a living human organism and invasion from the bacterial field The patient apparently was cured by sulfonamide compounds and penicillin How much the man's "will to live," or his emotional attitude, colored the picture could not be estimated

The second, a case of hermaphroditism, illustrated the powerful influence of xx and xy chromosomes on the faulty establishment of sex There existed as part of the error a great hypertrophy of the adrenal cortex A review of this problem led to critical discussion of certain psychoanalytic concepts of sex which refuse to accept the biologic point of view

In the third case the diagnosis was "anorexia nervosa" Such a term perhaps overemphasized the "purely psychiatric" basis of the patient's difficulty Observation of the patient from the standpoint of her constitutional status revealed many faults of growth and development These were interpreted as evidence of genetic faults in the quality of her protoplasm, which during the process of maturing had responded inadequately to the pressure of environment

The first patient nearly failed in his bacterial contest because of a specialized fault in his forces of immunity The second, incomplete creature expressed the futile result of specific failure in the organism's biologic phase of sex establishment The third patient was composed of poor protoplasm, poorly put together On this basis, physiologic functions generally were limited and unstable in capacity As part of the total physiologic fault, therefore, emotional disturbances arose

The discussion was focused on the subject of the whole organism, which is the patient, and, in consequence, on the necessity of properly balanced therapeutic technics appropriate to the full range of medicine

DISCUSSION

DR WALSH MCDERMOTT This paper of Dr Draper's is in effect a strong plea for the biologic approach to the study of man as an accessory before the fact, or really as a collaborator in the production of human disease

For centuries men have been studying the soul of man as something rather apart from his body Particularly during the last three hundred years there has been considerable study of economic man and political man, yet until quite recently the problems of man's inheritances and his struggles as conditioning factors in his diseases have been neglected save for the field of the so-called mental diseases That this should be so is not surprising when one considers both the immensity of the problem of man's diseases and the lack of notable success up to now in the study of political and of economic man Hence, one wonders why any one should seriously consider such a study

Yet there are several reasons that this study must be done First, as physicians it is our business to treat disease efficiently, and, as Dr Draper has pointed out, we can approach that efficiency only if we have perception of man's individualities and utilize that perception in modifying our treatment A more basic reason for the biologic study of man and his diseases is the fact that political man, economic man and diseased man are all the same man, and thus he cannot be trisected or otherwise subdivided I think it can be assumed that unless the next century or so gives more understanding of that man, specimens of him may be extremely difficult to obtain for study The field in which this study of man as an accomplice in the production of his diseases is most suitable for biologic study is that of infections This is despite the fact that, as the bacteriologists lament, there has been no systematic biologic study of the other half of the combination—the infectious agents which cause, or, perhaps it should be said, collaborate with man to produce the disease Until quite recently, unless a bacterium could ferment wine or kill a man, it received short shrift from the investigators In a limited sense the term "susceptibility" as applied to an infectious disease indicates whether the infectious agent can gain access to the host The degree of this susceptibility may vary all the way from complete susceptibility of the host to the opposite extreme Dr Draper uses the term "susceptibility," and I agree with him, to cover a larger state, that is, the total reaction of the host to the presence of the infectious agent In the study of infectious diseases, much work has been done on susceptibility in the limited sense A great deal of this work was done by Dr Draper himself, but, as I understand his thesis tonight, he implies that it is not enough, for example, to list whether the incidence of tuberculosis in Eskimos is high or low Rather, one must study why a particular agent in a particular man produces the particular clinical picture There are several approaches to this problem of the handling of human infections One is the approach of some public health officers Basically, they are interested in man solely as a spreader of disease For example, they have shown that the incidence of certain infections can be kept within proper bounds by the padlocking of all houses of prostitution, but they have given no thought to the resulting problem of the young man who comes to the city from an area where haystacks abound only to find that in the furnished room, which is all that he can afford, no companions other than men are permitted after dark

Another instance of the too limited approach to the problem of infection can be seen in the chemotherapeutist who in his zeal for the battle overlooks the battleground In the treatment of a patient ill with pneumococcic pneumonia and in shock, it is entirely possible to administer enough penicillin to sterilize the blood stream and prevent further extension of the local process in the lungs, only to observe the patient's shock become more profound, with resulting death I shall wisely refrain from defining the term "shock," as I think Dr Draper will refrain from a precise definition of "protoplasmic products" and as both Dr Draper and I would avoid a definition of "democracy"! Yet the point is that once a certain train of physiologic events has been set in motion by the struggle between parasite and host, the elimination of the parasite may not be sufficient to save the host And there is evidence at present to support the belief that among all the influences which contribute to that state of shock the variability of the individual man may play a role

One often encounters individual variations in the course of infections because men differ from each other It so happens that the fat girl in the case described by Dr Draper did not have an infection, but the phenomenon of the onset of clinical tuberculosis in an obese adolescent who has undergone drastic dieting because of ridicule is a sufficiently common observation The variation in the reaction of the human host to infection with syphilis is not alone between the extremes of many and of few morphologic changes In many cases the important disease to the patient is the bare knowledge of the infection itself Hence, even in the relatively limited field of the infections it is not enough to quarantine the infected man or to destroy the infecting organism, proper attention to the patient himself is essential for proper handling

As Dr Draper has presented it, these efforts at adjustment by originally imperfectly balanced and traumatized human beings may become the signs and symptoms of disease The effort to comprehend these efforts is a real challenge and one, as all here know, which he has not been afraid to accept

Dr Lawrence S Kubie I discuss Dr Draper's paper with many regrets I hate to see an honored banner carried in an unworthy cause, particularly when it is held aloft by one who in the past has done so much for a better cause I regret that I feel it is necessary to criticize unsparingly the doctrine which Dr Draper has expounded

Psychosomatic medicine is a search for correlations between the organic agents of disease and the role of psychologic forces in disease Important correlations of this kind are not to be sought in the rare and the exceptional case Indeed, if the use of the exceptional case is coupled with the implication that such correlations occur only in extreme cases and that no correlation can be expected with less spectacular ailments, one is likely to be blinded to the subtle interweaving of the organic processes of common diseases and the emotional stresses of everyday life It takes no great acumen and no special technics to understand that the psychologic development of a child with hypospadias will be different from that of a child with normal genital organs But it takes an open mind and highly trained technics to explore the correlations between emotional development and such everyday ailments as colds, allergies, troubles with the joints and heart disturbances Such a correlation goes far beyond a naïve emphasis on body form and its deviations (as illustrated by Dr Draper's cases) It demands a far subtler appreciation of human personality and physiology

Therefore, my first point is that the cases which Dr Draper presents are the freaks in the side show of the medical circus They are interesting, and they merit scientific investigation for their own sake, but they do not throw light on the fundamental problems of psychosomatic medicine

As a matter of fact, Dr Draper overlooks the clinical fact that in appropriate circumstances serious physical handicaps, whether lifelong or acute, may mask neurotic difficulties rather than intensify or expose them With a broken leg or an acute infection, even persons with frank psychoses may make temporary symptomatic recoveries This has long been known, and it is one of the strong arguments for the role of emotional factors in such diseases and against the irreversible nature of the changes which underly the psychosis None of this does Dr Draper consider

Furthermore, from what he has said, it would seem that he neglects such considerations because he has failed to grasp the importance of the fundamental concept of "symbolic trauma" He alluded to "symbolic trauma" with a slighting emphasis, which was in itself revealing He seems to be unaware that the body, its parts and its organs can represent emotional problems and that disturbances in these organs can be a sign language by which the patient attempts to discharge the energies involved in these problems I shall state without qualification that no one who has failed to grasp this fact understands even the elementary concepts of this important subject

Indeed, one of these days every physician will think of his patients and their illnesses in terms of symbolic trauma He will ask himself, "What does this broken leg mean to this man, consciously and unconsciously? What does this rash mean to the patient, consciously and unconsciously? What does this pain or this fever or joint mean on both these levels?" When every physician thinks of disease in this way, then for the first time in human history the physician will have become a mature healer of men That is why Dr Draper's slighting reference to the "symbolic trauma" is such an unfortunate and reactionary step

These, however, are all sins of omission Dr Draper is also guilty of sins of commission which are equally serious in that in every reference to psychoanalysis he distorts and misrepresents it This is of no importance to psychoanalysis, but it is extremely important to medicine, the future progress of which depends in no small part on the wise utilization of analytic knowledge and analytic technic in the study of organic disease I shall not take the time to dissect and expose all of Dr Draper's misrepresentations of psychoanalysis A few illustrations will suffice Psychoanalysis is usually, although mistakenly, attacked as encouraging licentiousness Dr Draper finds it too moralistic Psychoanalysis is also under attack for being "too biologic," i e, for neglecting "cultural forces" Dr Draper finds it to be insufficiently biologic Actually, both pairs of criticisms are based on ignorance The theory of libido (or instinct) is nothing else than a theory of the biologic basis of human behavior It is more than ignorant however, to lift out of its context a statement, such as the one by Freud which Dr Draper read Every one who is acquainted with psychoanalytic literature can cite a dozen places where Freud specifically said that with the gradual increase in understanding of biochemical forces and with the isolation of active biochemical agents the whole analytic process may be shortened But he always coupled this statement with a warning against premature and naïve efforts to correlate a biology which was still groping with an analytic psychology which was also fluid and formative Freud's position was always that until both disciplines were mature it was best for each to confine itself to its own technics Against such cautions no sensible scientist can protest, and in view of so many reiterated statements to this effect it is inexcusable to lift out of its context Freud's statement that in the discussion of sexual behavior he would limit himself to its psychologic aspects and to use that statement as evidence that Freud turned his back on biology

Finally, lest any one think that this criticism of Dr Draper's paper grows out of that blind orthodoxy of which psychoanalysts are so often accused, let me state that I have spent the last few years of my scientific life in criticizing psychoanalytic theory and psycho-

analytic technic and in attempting to modify both basically But, as a constant critic of psychoanalysis, I feel that I have the right to insist that such criticism be based on accurate knowledge and not on ignorance or misrepresentation

DR GEORGE DRAPER I have not much more to say, but it always gives me the greatest satisfaction to have Dr Kubie take issue It entertains me to cross swords with so brilliant a student of these problems This is not the first time that Dr Kubie has indicated that the selection of too extreme cases is dangerous If instead of "extreme case" one thinks of an "object of large size," it becomes easier to understand When one teaches children to read, one first shows them enormous *A*'s *B*'s and *C*'s, and as they grow older and comprehend the significance of the symbolism of these huge letters they are able to read in small details the significance of these original, enormous, letters Biology consists of a series of moving protoplasmic patterns which follow simple basic principles, and as the student becomes more and more accustomed to, and understands, these principles he begins to comprehend their significance Dr Freud was just a physician, like you and me, at first rather more occupied with chemistry than with medicine, but he was a doctor, a good, kindly man, who became interested in a point of view and decided that his point of view was better than the biologic one Perhaps it is, but in dealing with life, about which one knows very little, it is important to gather as much information as possible In the consideration of this whole subject, which has been unfortunately designated "psychosomatic medicine," words have been used with too little thought of their biologic connotation This dichotomous term does not contain the concept of a living, organismal unit I remember an old lady saying to me once, "Perhaps you ought not to investigate life, perhaps we are not supposed to know" Of course, intelligent people cannot follow that thesis; biology is an objective study of living nature Like religion, psychoanalysis is man made, a mental concept, based on a subjective interpretation of what man thinks about life

Relation of Life Situations, Emotions and Nasal Function

DR THOMAS H HOLMES (by invitation), MISS HELEN GOODELL (by invitation) and DR HAROLD G WOLFF

Daily observations on nasal function and structure, including changes in circulation, size of the turbinates, secretion and evidences of obstruction and pain, were made on healthy and on diseased persons Daily records were also made of the subjects' life situations, attitudes, dominant emotional reactions, effectiveness, energy, fantasies and dreams Chronologic relationships of the two sets of observations were then formulated The subjects could be classified as reactors and nonreactors in the sense that the changes in the nose in relation to life situations were far greater and more frequent in some persons than in others

Although swelling of the turbinates and mucosal vasodilatation often paralleled each other, there was also observed a dissociation of function, in that swollen turbinates were noted with mucosal vasoconstriction Mucosal edema and pallor sometimes followed prolonged mucosal vasodilatation

Chilling of the body surface (remote from the nose) was associated with initial mucosal vasoconstriction (pallor), swelling of the turbinates and increased secretion, followed by mucosal vasodilatation, prolonged swelling, increased secretion and obstruction, until the chilling was removed

Abject fear, dejection and disgust were associated with vasoconstriction, or pallor, of the nasal mucosa, decreased secretion and shrunken turbinates On the other hand, conflict with anxiety, resentment, frustration, anger and rage were associated with vasodilatation, or redness, of the mucosa, swelling of the turbinates, increased secretion and obstruction When the latter emotional states were sustained, the associated nasal changes, which were at first usually predominantly unilateral, became bilateral Also, when swelling and obstruction persisted, pain and tenderness sometimes occurred, spreading over the zygoma and into the temporal region

In a subject with a large gastric stoma, the circulatory changes in the nasal mucosa in various life situations inducing fear, disgust, anxiety, resentment, anger and frustration paralleled those in the gastric mucosa

Frank weeping, as well as the feeling of being "on the verge of tears," associated with frustration and resentment was accompanied with pallor and extreme swelling of the nasal mucosa, profuse secretion and obstruction, with complaints of difficulty in breathing These observations indicate the relation of such sustained swelling, vasodilatation, increased secretion and obstruction with pain to disease of the nose and the paranasal spaces

DISCUSSION

DR GERVAIS WARD MCAULIFFE In my capacity as consultant to the Payne Whitney Clinic during the past twelve years, I have had a rare opportunity to see the close relation between emotional disturbance and function of the nasal structures Routine examinations of the ears, nose and throat are made on approximately 500 patients a year To obtain a cross section of this group, I selected at random 50 charts and summarized the observations on the nose, together with the psychiatric diagnoses Briefly, the data may be summarized as follows

Of the 50 patients, only 2, or 4 per cent, had an essentially normal nasal condition Forty-seven, or 94 per cent, had hypertrophy, and injection of the turbinates of varying degrees, and 35, or 70 per cent, had "cloudy" sinuses on transillumination Twenty-eight, or 56 per cent, had specific complaints referable to the nose In 35 patients with a condition diagnosed as a psychosis "depression" was a feature In 12 patients weeping was a persistent and serious symptom, and 3 of these complained that they could not breathe through the nose

In a large number of patients I have seen in my office the complaints referable to the nose were but one manifestation of their basic problems For instance, a young married woman aged 26 came to me in March 1944 with a copious watery nasal discharge and the complaint that she could not breathe through her nose Five years ago she had had similar symptoms in a setting of dissension in her family and the death of a dearly beloved older friend A submucous resection was done by a competent otolaryngologist The complaints of March 1944 began in August 1943, in the third month of her second pregnancy, when her husband enlisted in the Navy and was given a deferment from active duty until two weeks after the birth of their child. At the same time her obstetrician told her that she had a weak heart and that she would not be able to take an

anesthetic during labor Her local physician assured her that her swollen, engorged and dripping turbinates were a feature of her pregnancy and that her discomfort would end with the delivery of her baby The symptoms continued, however, and grew worse with her loneliness and her unhappy, insecure situation, separated from her husband She was found to have no special allergies, but she was desperate for relief from her discomfort and confidently expected and hoped for an operation—which I was sure would not solve her difficulties To make a long story short, in April she found a place to live adjacent to her husband's post on the New England coast, and she is now with him in Boston Her symptoms began to improve in May, and in her last report to me, at the end of August, she said she was well

The observations reported by Dr Wolff and his associates are therefore in keeping with the everyday experience of the otolaryngologist and should stimulate an interest in the broader aspects and implications of nasal disease

Dr George Draper Dr Wolff's discussion has interested me considerably Five or six years ago a small town practitioner in New England wrote a provocative paper about changes in color of the nasal mucous membrane in relation to emotional disturbances, unfortunately, I have forgotten the reference Dr Wolff omitted to state that when the dog-faced baboon becomes emotionally disturbed evidence of that disturbance is reflected in a change in the color of the mucous membrane of the animal's rear end

Dr Oskar Diethelm I wish merely to draw attention to the fact that this subject was first mentioned by Peyer, who had been influenced greatly by Beard's concept of neurasthenia and the discussion at the gynecologic congress in Washington, D C Peyer pointed out that in patients suffering from sexual disturbances due to coitus interruptus he frequently noticed rhinitis He discussed this relationship in the *Munchener medizinische Wochenschrift* in 1889 I mention this because it shows that these problems have been noted for a long time and were discussed by various authors before Freud's formulation Another article, by Mackenzie, a nose and throat specialist, appeared in the *Bulletin of the Johns Hopkins Hospital* in 1898 Again, the sexual factor was stressed exclusively Further literature on this topic can be found in Halban and Seitz's "Biologie und Pathologie des Weibes Ein Handbuch der Frauenheilkunde und Geburtshilfe" (Berlin, Urban and Schwarzenberg, 1937) Dr Wolff has presented a much broader aspect of the problem, stressing the importance of emotions It is interesting to note how little has been published on this topic Only in recent years has the part which emotion plays in these disturbances of nasal function been brought out, and never as clearly as Dr Wolff and his associates have done

Dr George E Daniels In line with Dr Diethelm's observation on the literature concerned with the relation of sexual malfunction and the nose, it is of interest to mention some of the work on the association of the nose and hormonal changes Mortimer, Wright and Collip (Effect of Administration of Estrogenic Hormones on Nasal Mucosa of Monkey, *Canad M A J* **35** 615, 1936) made observations on 60 pregnant women and found that in 60 per cent of them there was a noticeable swelling of the nose, which increased and reached its height in the ninth month, coincident with the peak of excretion of estrogen in the urine In observations and experiments on rats in connection with pseudopregnancy, it has been found, among other things, that not only electric stimulation of the head but, in certain instances, the use of a solution of silver nitrate on the nasal mucosa will bring about pseudopregnancy (Shelesnyak, M C, and Rosen, S Naso-Genital Relationship Induction of Pseudopregnancy in Rats by Nasal Treatment, *Endocrinology* **23** 8, 1939) Dr Draper has commented on the changes in baboons It is also of interest that in monkeys with the change in sexual skin which comes at the time of increased sexual stimulation changes have also been noticed in the mucosa of the nose (Mortimer, H, Wright, R P, and Collip, J B Effect of Administration of Estrogenic Hormones on Nasal Mucosa of Monkey, *Canada M A J* **35** 503, 1936)

All this shows that the problem of emotional changes in nasal function is a complicated one, and Dr Wolff and his associates have made extremely valuable observations in regard to this function Later, when all the data can be considered together and it can be determined to what degree hormonal changes and sexual conflict may enter in, one may come nearer the solution of the problem

Dr John Galloway Lynn I want to ask Dr Wolff about a matter which he did not emphasize in his interesting talk but in which I am especially interested because of its parallel nature to some work I was associated with, that is, the laterality of the effect on the mucous membrane of the nose in 1 of his patients In this patient, he noted that during euphoria, an almost hypermanic state, the right side of the nose was swollen, congested and red and that when the man's emotional state became normal the nasal condition subsided I think that with the swelling on the right side the left side was pale Several years ago, at the McLean Hospital, Waverly, Mass, I noted the same phenomenon of laterality in conjunction with the emotional expression of two sides of the face in a manic patient He had noticeable hyperactivity of the right side of his face during the manic phase, and during the depressed phase which followed, the emotional expression shifted over to the left side, with a definite blankness on the right side The shift of symptoms from one side of the nose to the other with the change from euphoria, or hypermania, to the depressed state is interesting, since it parallels the observation of a similar shift in facial expression which I made several years ago

Dr Harold G Wolff As Dr Lynn pointed out, unilaterality of reaction of the nasal mucosa is a feature When the reaction is sustained long enough, as for several days, there is a fluctuation of increased redness, swelling and secretion from side to side, but during such a persistent reaction the signs and symptoms on each side increase in magnitude and intensity This is what we observed in the patient I described Second, the same man had occasional unilateral migraine headaches on the right side We have examined his nose during these headaches, and the reaction in the nose was homolateral

Lastly, as to the relation between sexual function and the nose, I left that out on purpose, because, as Dr Diethelm points out, the earlier studies dealt with sex as if it were purely an erotic reaction We have made observations (incomplete as you may guess) on the nose before and during the sex act There are redness, dilatation, swelling and increased secretion In the adolescent, in whom masturbation is often coupled with

a sense of guilt, similar reactions occur I am not at all certain that what one sees in supposedly sexually excited people does not represent as well reactions accompanying conflict and a sense of guilt

I am grateful to the discussers

Incidence of Infections of the Upper Respiratory Tract in Relation to Emotional Reactions and Adjustment

DR J LOUISE DESPERT (by invitation)

In an attempt to study the psychosomatic factors involved in the incidence of infections of the upper respiratory tract, the records of 63 children (32 boys and 31 girls) admitted to the Payne Whitney Nursery School from 1937 to 1942 were analyzed The records include anamnestic data, reports on physical examinations and psychometric tests, daily behavior records and records of individual play sessions

In the process of analyzing the total body of data, it was found that in the group with the highest incidence of respiratory infections there were, besides the 8 children from broken homes, a large number with emotional stresses due to other causes than disruption of the home and a few children who were free from such stresses Conversely, there were a few children who, while presenting emotional problems, were conspicuously free from colds There were more boys than girls among the children with the highest incidence of colds Finally, from the pediatricians' reports it was not possible to differentiate positively between toxic and allergic colds

Several observations stand out as significant. First, in the total group of 63 children, of equal sex distribution, there were more boys than girls among the children who had more frequent infections of the upper respiratory tract Second, in the group with the highest frequency there were more children who showed persistence of infantile traits, especially those of an oral aggressive character, and more who had difficulties in adjustment In this group there were also more children with speech deviations and slightly more in whom bladder training was achieved late While the number of cases is too small to have statistical value and significance, the psychodynamics in individual cases indicate certain trends

Saul (*Internat J Psycho-Analysis* **19** 451, 1938) reported on 15 patients who came for psychoanalysis because of neurotic symptoms but whose early history showed a high frequency of colds In 9 of them, colds occurred in "situations of frustration of strong, mostly unconscious, receptive demands with more or less repressed rage"

Studies on stuttering (Despert, J Louise *Am J Orthopsychiat* **13** 517 [July] 1943) also bring out the close correlation between repressed hostility and symptoms involving the upper respiratory and upper digestive tracts

As seen in the group studied, repressed hostility can be manifested in some children by somatic symptoms, of respiratory nature, while in others with similar psychologic factors operating there is total absence of respiratory symptoms and in still others various somatic or neurotic symptoms may be noted The choice of symptoms involves complex considerations, to a large extent related to the earliest emotional experiences in infancy Since problems of internal tensions are more common in boys than in girls, it is possible that there is a fundamental sex difference between infants, a difference which may bear in particular on one of the earliest aggressive drives, namely, aggression through the oral zone Where the aggressive drive is greater, there is more chance for thwarting through training or inadequate mother-infant love relationship Careful studies of individual and sex differences in infants will offer valuable leads to an understanding of their later adjustment in terms of psychosomatic expression

DISCUSSION

DR WILLIAM DOCK I shall consider only one point in connection with this discussion, assuming for the moment that the data which have been collected really indicate that the children under discussion had more colds Actually, the data could mean that the parents kept the children home with fewer symptoms At present I do not believe one can say whether these children were kept home with fewer symptoms than other children or whether actually they had more, or longer-lasting or more severe colds I should like to point out that in considering the nose the somatic constitution cannot be ignored Grant and Mudd, who were the first to show that the nasal mucous membrane reacts with the skin, becoming hyperemic when the skin is hyperemic and pale when the skin is pale, found that there are great individual variations Some people turn red when they are angry, and some people turn pale, and so do their noses Some people respond strongly and other people very little, this observation has been confirmed in Germany by an otolaryngologist who made studies with a thermocouple on a group of patients, using the same cold stimulus that Grant and Mudd had employed He found that some persons had pronounced vasoconstriction and others had almost none Such persons would correspond to the reactors and the nonreactors described by Dr Wolff When the patients were questioned by another physician in the clinic who knew nothing of the vasomotor reactions, it was found that the subjects who reacted strongly with vasoconstriction were persons who experienced a great many infections of the upper respiratory tract and that those who did not react had few such infections This means that if the children from families which had been arbitrarily broken up reacted in this way there must have been an inherited factor which made most of them reactors In the good old days people were divided into the cold and the dry, the hot and dry, the cold and wet and the hot and wet type, the persons of the type under discussion here are the pituitous people, the cold and wet people, who break up their homes and move around with little consideration for others and who are classically described as having "running noses" The children with "running noses" did not inherit a disturbing situation only, they inherited genes which predispose them to nasal misbehavior

Dr Despert's figures show there was a tremendous increase in infections of the respiratory tract in December, January, February and March, with a sharp falling off in April and May, and that in the early months of the fall these illnesses were few In the early months of the fall the stresses placed on children from their being thrown into the school environment must have been maximal, in spite of that, it was not until the weather became cold that the children had colds Therefore, these emotional factors must combine with the vasoconstrictor effects of a cold climate to predispose to infection of the upper respiratory tract, and, after all, then only in suitably constituted persons

If it is found that there is a correlation between these factors, it will have to be concluded that people break up their families largely because they are apt to have children with running noses!

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb 23, 1945

GEORGE D GAMMON, M D, *Presiding*

Localizing Value of Temporal Crescent Defects in the Visual Fields

DR H A SHENKIN and DR I R LEOPOLD

This paper was published in full, with discussion, in the August 1945 issue of the ARCHIVES, page 97

Resection of the Superior Longitudinal Sinus

DR. RUDOLPH JAEGER

In 1942 I reported 10 cases in which I resected a portion of or ligated the superior longitudinal sinus for the complete removal of parasagittal meningioma (ARCH NEUROL & PSYCHIAT 48 977 [Dec] 1942) In that series I reported the only case in which an unoccluded superior longitudinal sinus was resected at the rolandic inflow of veins, in this case the patient died, although the tumor was tiny This was the only death in the series, although in 5 of the cases the tumor was much larger, completely occluded the sinus and was situated either at or posterior to the rolandic inflow From these cases, and from 15 others collected from the literature, it was concluded that resection of the superior longitudinal sinus at any point should not be dangerous provided the vessel already had become occluded by being slowly filled, so that adequate collateral venous circulation had developed

A fatal case similar to the one in the first series is now recorded A second surprising case is also reported in which the sinus was ligated back of the rolandic inflow and anterior to the torcular Herophili, where the sinus was not occluded, the favorable outcome indicating that ligation at this point is safe

CASE 1—*Resection of meningioma with a portion of the superior longitudinal sinus at the rolandic inflow with fatal outcome*

Two years previously a man aged 39 had had a tumor of the left parietal lobe incompletely removed A second operation was performed on Sept 25, 1944 because of exacerbation of signs and symptoms referable to the right motor area A large, boggy, vascular meningioma was isolated from the cortex of the brain It was a long, bilobed mass, lying tightly against the sinus and apparently infiltrating it Three weeks later the sinus was uncovered and thoroughly inspected and palpated It appeared that the tumor was completely occluding the sinus After the large rolandic veins had been coagulated and severed as they entered the sinus on the right side, about 5 cm of the sinus and the entire tumor were removed in one mass The operation was performed without shock, and the patient's condition was good the next day However, he failed rapidly and died on the fourth postoperative day Permission for necropsy was not obtained On opening the resected sinus, it was found that space existed for the passage of blood past the tumor protruding into the lumen

The fatal outcome in the second case definitely indicates that removal of an unoccluded superior longitudinal sinus cannot be safely performed

CASE 2—*Resection of superior longitudinal sinus between the rolandic inflow and the torcular Herophili, with uneventful recovery*

A man aged 39 presented the complaints of nuchal pain, headache, blurring of vision and general weakness Examination showed that the patient was somewhat stuporous, with choked disks, left homonymous hemianopsia and weakness of the left arm and the left side of the face A tumor of the right occipitoparietal region was suspected and an appropriate craniotomy performed A dense meningioma, weighing 99 Gm, was resected from the sinus midway between the rolandic inflow and the torcular A portion of it was seen to enter the sinus and was not disturbed It appeared to occlude the vessel completely

Eleven weeks later it was decided to remove the involved portion of the sinus with the remaining tumor A second bone flap was turned over the site of the tumor to expose the sinus adequately Palpation of the sinus seemed to indicate complete closure of the vessel by a nodular mass The sinus was tied off above and below the nodule and resected Examination of the removed specimen revealed that the vessel was still patent, although the tumor filled approximately three fourths of the lumen Convalescence was uneventful, and the patient has completely recovered except for hemianopsia

From this case one can conclude that ligation of the superior longitudinal sinus between the rolandic inflow and the torcular Herophili is safe and should be done when a tumor which invades this structure cannot otherwise be removed

From these 2 cases and the 25 cases previously reported, one may now conclude that the superior longitudinal sinus may be ligated anterior to the rolandic inflow of cortical veins at any point without risk Ligation at the rolandic inflow can be safely performed only when the sinus has been completely occluded by a tumor Ligation between the rolandic inflow and the torcular Herophili can be done even though the sinus may still be patent

DISCUSSION

DR HENRY T WYCIS I should like to ask Dr Jaeger first whether or not he has ligated the rolandic vein alone without disturbing the superior longitudinal sinus Second, has Dr Jaeger conducted any animal experiments with the use of stainless steel plates? Dr Michael Scott and I have started a series of animal experiments on the repair of defects of the skull with stainless steel plates This work is unpublished

DR WALTER FREEMAN, Washington, D C Has Dr Jaeger made any arteriographic studies in these cases to determine the condition in the anastomotic veins and in the dural sinuses?

DR RUDOLPH JAEGER I have made no angiographic studies in these cases One might try such a study when a tumor is suspected to involve the sinus, taking the roentgenograms at the venous phase of the injection This method may be worthy of trial in future cases Better still might be the injection of a dye directly into the sinus at operation, with roentgenograms taken with a portable machine This should

show whether or not a nodule is closing the lumen of the sinus

DR HENRY SHENKIN My associates and I have had some experience with cerebral angiograms and second phase venograms at the University Hospital I do not think that one would be able to see whether the superior longitudinal sinus was thrombosed or not Often one does not see the vessel at all in presumably normal angiograms

DR WALTER FREEMAN, Washington, D C I think that if the roentgenogram is taken late enough one will be able to see it Dr Rowe and I presented a paper on arteriography in which that point was emphasized

DR FRANCIS M FORSTER The section of the brain Dr Jaeger showed demonstrates well the limits of damage to the cortical gray matter resulting from occlusion of the superior sagittal sinus It is interesting that pathologically the white matter is not involved by thrombosis or occlusion of either the superior sagittal or the straight sinus, whereas occlusions of both these structures involve the cortical gray matter, the basal ganglia in part and the intervening white matter This is compatible with Schlesinger's observations on the venous drainage of the white matter

In regard to Dr Jaeger's suggested procedure of introducing a small catheter into the superior sagittal sinus to determine whether or not occlusion was complete, I wonder if he has considered the possibility of thus producing an air embolus and if he has considered any methods for circumventing this

DR RUDOLPH JAEGER As far as I can ascertain, the rolandic cortical veins entering the superior longitudinal sinus can be ligated when the situation is normal on one side, as when one is approaching the third ventricle and the pineal recess When the sinus is ligated, it closes both rolandic inflows and causes certain stagnation of the circulation of both hemispheres in a great part

With regard to stainless steel plates for closing the skull, I had occasion to remove one of these which I had put in several years before It was just as bright as when it was inserted We have used stainless steel wire to close bone flaps many times It stays bright and shiny, and there is no tissue reaction to it In opening large veins for any purpose one must be careful not to get air into them This is the reason I prefer some type of injection of dyes

As to the question whether one can ligate the superior longitudinal sinus anterior or posterior to the rolandic veins, as nearly as I can make out, it is a safe procedure provided the rolandic veins are not ligated

The Vasomotor Component of Labyrinthine Vertigo

DR E A SPIEGEL, DR G C HENNY and DR H T WYCIS

An analysis of the syndrome of vertigo has to take into account not only the disturbances of orientation produced by labyrinthine stimulation but the secondary effects of rhombencephalic vestibulovasomotor reflexes on the cerebrum In experiments on cats, the cerebral circulation was recorded thermoelectrically on labyrinthine stimulation With all types of stimulation used (calorization, galvanization, rotation), slowing of the cerebral blood flow accompanied the fall in systemic blood pressure This reaction, as well as the retardation of the cerebral blood flow on stimulation of centripetal vagal fibers, is chiefly brought about indirectly through the changes in the systemic circulation, since both reactions persisted after interruption of the cervical sympathetic nerve fibers and/or the vasodilator tract joining the facial and the great superficial petrosal nerve Since impairment or fluctuations of the cerebral circulation may give rise to sensations akin to vertigo, the role played by vascular reactions in the mechanism of labyrinthine vertigo should not be overlooked

DISCUSSION

DR GEORGE D GAMMON I should like to ask Dr Spiegel what degree of fall in blood pressure was noted in these experiments and whether vertigo may be the result of fall in systemic blood pressure, with a secondary fall of the cerebral blood flow, or the result of vestibular stimulation Patients who do not have a sense of directional movement perhaps have only minimal stimulation of their semicircular canals Is this not also a factor, as well as the fall in blood pressure?

DR HENRY T WYCIS I should like to speak of the technical details involved in this work In order to dislodge the otoliths from the maculas, it is necessary to rotate the guinea pigs at a rate of 1,000 to 2,000 per minute Breathing probably ceases during rotation, so that artificial respiration is necessary as soon as the animals are removed from the centrifuge Another interesting point is the recording of blood pressure in a guinea pig The carotid artery is cannulated with a fine glass tube, and the animal is heparinized to prevent clotting in the cannula This is indeed a tedious task and requires skill and patience

Dr Spiegel has been the first to show that one can elicit a fall in blood pressure by various methods of labyrinthine stimulation Furthermore, he has shown that the fall in blood pressure is abolished not by section of the vagus nerve but by section of the cervical portion of the cord

Some years ago, in an interesting paper, Wotzilka showed that a similar mechanism is present in man By rotating patients on large tables he was able to show two types of blood pressure reactions One group of patients showed an initial fall in blood pressure, while the second group presented the same reaction which was demonstrated in the animal experiments, namely, an initial fall followed by a secondary rise

DR E A SPIEGEL The fall of the blood pressure is between 10 and 20 mm, similar to the effect produced by stimulation of the depressor fibers of the vagus nerve

The question whether minimal stimuli may fail to produce ocular reactions but may produce vegetative reactions is a complicated one I should like to say this Seasickness or airsickness is certainly a type of stimulation of the labyrinth, since persons with unexcitable labyrinths are immune to motion sickness Sjoberg had the idea that if one applies fine enough methods of recording one may find some reaction of the eyeballs That may be possible, but on simple observation one does not note ocular reactions I think the explanation for this may be sought partly in the following direction The type of stimulation on shipboard is somewhat different from that in the Barany chair test If one rotates the patient in the chair in but one direction, one produces a flow of endolymph and a deviation of the cupola, as has been done in animals, particularly by Steinhausen Under these conditions one gets ocular reactions If a person is on a boat and the boat is

rolling for a few degrees to the right and then a few degrees to the left, there is a deviation of the cupola, first in one direction and then in the opposite direction Hence, the type of stimulation in such a case is rather different from the stimulation on a rotating chair In the Barany test one has a deviation of the cupola and, in the example mentioned, an oscillation around the resting point Thus, there are types of stimulation of the semicircular canals that may produce vegetative, but not ocular, reactions In up and down movements of a ship, one deals chiefly with otolithic stimulation

With regard to the role of the splanchnic nerve, I should say that it explains only part of the mechanism In experiments several years ago, my associates and I made transverse sections of the cervical or the upper thoracic region of the cord, and after these sections we were not able to produce a fall of blood pressure on labyrinthine stimulation However, when we raised the blood pressure or prevented its fall after section of the cord, the blood pressure was still influenced by labyrinthine stimulation Probably the reaction of other vascular areas also plays a part in this mechanism

Book Reviews

Experimental Basis for Neurotic Behavior Origin and Development of Artificially Produced Disturbances of Behavior in Dogs. Psychosomatic Medicine Monographs Vol. III By W Horsley Gantt, M D Price, $4 50 Pp 210, with 52 illustrations New York Paul B Hoeber, Inc, 1944

This monograph represents studies on the nervous disturbances of dogs conducted over a twelve year period at the Pavlovian Institute of the Phipps Psychiatric Clinic The book is sponsored by the American Society for Research in Psychosomatic Problems, Inc

After a short outline of the Pavlovian concepts and of the methods used in this laboratory, the author proceeds to describe in detail the histories of 3 dogs observed for three, five and twelve years, respectively, and subjected to the same experimental routine All the dogs showed disturbances in behavior when under stress, but these disturbances were only temporary in 2 of the animals The third dog did not recover but showed a spread of the disturbance to include other physiologic functions previously not affected and not directly connected with the experimental setting

The author stresses the existence of "personality" types in dogs which react to stress in a manner dictated by the type itself and which tend to exaggerate the essential characteristics of the reaction He indicates the possibility of detecting the existence of a conflict by changes in the interrelationship of several conditional reflexes before the overt behavior of the animal becomes disturbed He shows the reciprocal relation of sexual satisfaction or social contact to its effect in diminishing anxiety However, a most interesting observation seems to be that the conditional stimulus based on the unconditional reflex connected with food may become pathologic through conflict It may then be ameliorated, or even abolished, by subsequent association of the same stimulus with another unconditional reflex, such as pain

In a stimulating chapter, Dr Ischlondsky gives an analysis of the disturbance in behavior of the dog which was observed for twelve years While his analysis is based on the Pavlovian viewpoint, a psychologic explanation of the same facts by Dr Leon J Saul, based on freudian views, and another by Dr R Leighton, from the standpoint of the socioanthropologist, add to the interest and merit of the book The discussion shows that these explanations are not mutually exclusive and tends further to elucidate various aspects of the experimental data

The book is highly recommended because the presentation is clear and the material itself is thought provoking The observations are careful, and their evaluation is scrupulously honest The book's organization makes frequent repetitions unavoidable, but this does not detract from its interest

The Care of the Neurosurgical Patient, Before, During and After Operation By E Sachs Price $6 Pp 260, index and illustrations St Louis C V Mosby Company, 1945

This little book describes the standard technical procedures and equipment used in neurologic surgery at the author's clinic The general outline of history taking is given, and the details of special procedures, such as lumbar puncture, myelography and ventriculography, are described in detail The technic of various typical operations is also given Extremely valuable is the description of some of the finer points in postoperative nursing care

It is a highly personal book, as befits a publication from the hand of so experienced a surgeon Electroencephalography is briefly dismissed as a technic in the experimental stage, and while lumbar puncture is mentioned, little guidance is given to the interpretation of results The Wilkens technic of intradural approach to the gasserian ganglion is advocated The discussion of the indications for exploration for herniation of the intervertebral disk is refreshingly direct and easily understood

This is an excellent book for beginners in neurologic surgery

The Marihuana Problem in the City of New York Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana Price, $2 50 Pp 220, with 33 tables and bibliography Lancaster, Pa Jacques Cattell Press, 1944

While the smoking of marihuana is rather widespread among the intellectually and emotionally immature population concentrated in the vicinity of Harlem, the Mayor's Committee on Marihuana finds little cause for alarm The addict knows when he has had enough and refuses an overdose He does not crave the drug and shows no withdrawal symptoms, relatively little elevation in tolerance, even after a decade of constant use, and little tendency to lapse into severe alcoholism, morphinomania, crime or sexual excesses The addict employs it for the purpose of enjoying a quiet sociability, with lowered inhibitions and free-ranging philosophic speculations, which are actually on a very superficial level Mental and emotional deterioration are not demonstrable This is not to say that there are no toxic properties in marihuana Acute intoxication can result from overdosage, and psychotic states may follow acute intoxication, but these clear up within a few days

The Mayor's Committee, made up of outstanding investigators in various fields, has done a notable service in relieving the minds of worried citizens, who were all too likely to take their notions from the Sunday supplements and the rather lurid accounts of the effects of self-administered overdoses by the "romanticists" Clinical studies, superbly controlled, covering medical, neurologic and psychiatric, psychologic, physiologic and sociologic aspects of the problem of marihuana intoxication, are presented in several chapters The pharmacologic study, by Dr S Loewe, is a monograph in itself, opening up a whole new field of compounds (sixty-five) in the class of cannabinols It makes heavy reading for a psychiatrist, but it points the way toward further studies on possible therapeutic applications Cannabis indica was dropped from the "Pharmacopeia of the United States" in 1920, but no definite reason is presented for its reintroduction at the present time

Psychiatry in Modern Warfare By Edward A Strecker, M D, and Kenneth E Appel, M D Price, $1 50 Pp 88 New York The Macmillan Company, 1945

Now that the war is over, one may expect the literature on military neuropsychiatry to turn to efforts to sum up the emotional effects which modern warfare has on civilians and soldiers, to evaluate how the psychiatric problems were recognized and managed, and to be concerned with the inadaptability of some soldiers to return to civilian life In a sense, then, this little treatise may be considered a forerunner of such a trend

Though the book is small, its scope is large, and the authors rely on well chosen reports from the literature, reenforced by their personal observations, for the substance of the contents They lay chief emphasis on predisposition as an etiologic factor in neuropsychiatric conditions They note no new clinical entity except Mira's "psychorrhexis" in civilians The psychosomatic developments and the special problems arising from geographic considerations are mentioned

The trend away from anatomic pathology, prevalent in World War I, toward a more accurate, dynamic psychopathology is evident The new advances in treatment reflect this advance in the scientific use of narcosynthesis and group therapy

All this, and many other points, are briefly and clearly presented, making the book easy reading Its brevity has the disadvantage of slighting points which bear extension, for instance, the program of preventive psychiatry in the armed services, a truly significant advance, rates only a short paragraph

The section on problems of demobilization stresses the view that every soldier has an adjustment problem and offers advice which boils down to a list of "do's and don'ts," of small educational value

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HISTOLOGIC CHANGES IN THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

VII ALTERATIONS IN NERVE CELLS

CARL W RAND, M D, AND CYRIL B COURVILLE, M D
LOS ANGELES

In a series of studies concerned with pathologic changes in the various cytologic elements of the brain following injuries to the head, of which this study constitutes a unit, we have kept two objectives in view The first, and perhaps the most important, has been an attempt to explain the residual symptoms which so often persist after an injury to the head The second, and more academic, objective was an attempt to discover the finer details of such alterations which occur in these various elements as a result of craniocerebral trauma By a study of such changes it was hoped to shed some light on the biologic behavior of these cells and fibers in response to physical injury As these studies have drawn to a close, it has become evident that we have been more successful in the attainment of the second than of the first of these objectives In fact, it may be said that what has been learned regarding the clinical effects of trauma from our pathologic observations has been in a sense a by-product rather than the achievement of a primary objective Among the other reasons for this situation is the difficulty in the interpretation of the relative seriousness of multitudinous and complex lesions so often found after fatal injury It is, furthermore, often difficult to sort out the individual effects of the various processes initiated by such an injury Since these studies have been concerned largely with cases in which death occurred within a few days after injury, one's viewpoint of possible ultimate residual manifestations would necessarily be prospective

The previous studies in this series to date have brought to light facts which may be stated as follows

1 After injury there are an increase *in volume* of the epithelial cells of the choroid plexus and ependyma and an associated increase in cellular vacuolation The vacuoles themselves are larger than in ordinary circumstances and are increased in average number in the cell [1] If these changes are indicative of increased secretory activity, as we believe, the source of increased amounts of cerebrospinal fluid, as found clinically, is at least partially accounted for

2 After death from injury to the head, there is also found an acute swelling of the oligodendroglia cells, particularly those in the white substance of the brain, together with a generalized increase in the number of these cells, the latter being a result of an active direct cell division The vacuoles in the oligodendroglia cells apparently represented accumulations of fluid within the cell [2] This change has been interpreted by us as a response to increased amounts of fluid within the nerve tissues (true cerebral edema)

3 There seems to be no specific generalized response of the microglia to injury Activity of this element depends on actual destruction of tissue, as observed with focal injuries, such as contusions or lacerations [2] Their action is essentially phagocytic and is provoked by the presence of free blood in the tissues or by disintegrating nerve elements

4 Likewise, no generalized response of the astroglia elements is found as an acute response to injury About local contusions and hemorrhages there is a limited response of these elements, as manifested by their proliferation to form a feeble astrovascular scar [3] We do not believe that these local changes can have any serious effect on cerebral *function*

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1 Rand, C W Histologic Studies in the Brain in Cases of Fatal *Injury to the Head I* Preliminary Report, Arch Surg **22** 738 (May) 1931 *Rand, C W*, and Courville, C B II Changes in the Choroid Plexus and Ependyma, ibid **23** 357 (Sept) 1931

2 Rand, C W, *and Courville, C B* Histologic Changes in the Brain in Cases of Fatal *Injury to the* Head III Reaction of Microglia and Oligodendroglia, *Arch Neurol & Psychiat* **27** 605 (March) 1932

3 Rand, C W, *and Courville, C B* Histologic Changes in the Brain in Cases of Fatal *Injury to the* Head IV Reaction of the Classic Neuroglia, Arch *Neurol & Psychiat* **27** *1342* (June) 1932

The remainder of the studies in this series have been concerned with the parenchymatous elements These investigations have given a broader insight into the possible causes of the nervous and mental manifestations so commonly observed in patients who have had cerebral injury The essential observations in these studies are indicated herewith

1 Cerebral symptoms may be the result of an interruption of nerve fibers, as well as the effect of injury to the cells themselves The commissural fibers of the brain may be interrupted by the occurrence of small petechial hemorrhages, either within the corpus callosum or in its radiations Association and projection fibers may also be severed by subcortical traumatic hemorrhage, either primary in origin or secondary to local contusions The degeneration of nerve fibers originating in portions of the cortex destroyed by contusion explains the atrophy of the white substance and the enlargement of portions of the ventricular system observed consequent to such lesions [4]

2 The disturbance in the arrangement of the cortical nerve cells may be due to macroscopic or microscopic lesions The amount of tissue loss depends on the degree of the injuring force and the extent of its concentration As a rule, the location of gross cortical contusions following traffic accidents is such as not to cause focalizing symptoms other than impairment or loss of smell consequent to subfrontal lesions resulting in injury to, or destruction of, the olfactory bulbs Nerve cells retain their morphologic identity remarkably close to the margin of the injured area, the local injury destroying these elements only within and in the immediate margin of the lesion [5]

With these observations in mind we now turn to the more detailed study of the nature and extent of injury to the nerve cells themselves

It seemed advisable, because of the clinical manifestations which are to be accounted for on the basis of injury to nerve cells, to consider such post-traumatic alterations as (1) general changes, such as might account for the immediate loss of consciousness after injury (commotio cerebri), and (2) local changes, which are due to compression by dural hemorrhage or to local traumatic lesions of the brain, such as contusions, lacerations and hemorrhages (which explain the occurrence of localizing phenomena)

MATERIAL AND METHODS OF STUDY

The material used in this study was the same as that utilized in previous investigations, viz, blocks of tissue taken from the brain in 39 cases of fatal injury to the head This material was forwarded to the Cajal Laboratory for our use through the courtesy of Dr A F Wagner and Dr John H Schaefer, former coroners surgeons for Los Angeles County The bodies had all been embalmed within ten hours after death, and all but five of them within five hours This prompt fixation was an assurance of well preserved tissue, in which postmortem changes were reduced to a minimum After their removal from the brain, the blocks of tissue were further fixed in solution of formaldehyde U S P diluted 1 to 10 Sections from selected blocks were prepared with the hematoxylin and eosin stain, Herxheimer's method for fat, Mallory's phosphotungstic acid hematoxylin and aniline blue methods, cyanin and toluidine blue methods for tigroid material and Cajal's reduced silver method and Bielschowsky's silver method for neurofibrils

GENERALIZED TRAUMATIC ALTERATIONS IN NERVE CELLS

That generalized changes in the nerve cells of the brain occur after injury to the head had long been recognized although the degree of such changes, their significance in terms of disturbance of function and their possible duration after the initial injury have never been accurately established While it is too much to expect that all the answers to questions that might be posed are to be found in a study of the cerebral and cerebellar cortex in persons who have died of a craniocerebral injury, it is not unreasonable to suppose that such studies may at least shed a little light in a hitherto dark corner It is our purpose, therefore, to examine such changes and after viewing them in the light of experimental investigations which have been made at the hands of several students of the problem, to note their possible connection with the clinical picture which is widely known as "concussion"

A study of the problem in its initial phases brought to light the momentarily disturbing fact that there are two conditions which may be provoked by the general effects of injury and which must be separated if any adequate evaluation of the changes observed were to be made (1) the immediate effects of injury, which are known as commotio cerebri, or "concussion," and (2) the delayed effects of such an injury in the form of cerebral edema By utilizing what is known of certain changes in the nerve cells (essentially in the formation of vacuoles) which occur in the presence of edema of the brain, we have tried to distinguish between the changes suggestive of the abnormal collection of fluid in the cell and altera-

4 Rand, C W, and Courville, C B Histologic Changes in the Brain in Cases of Fatal Injury to the Head V Changes in the Nerve Fibers, Arch Neurol & Psychiat **31** 527 (March) 1934

5 Rand, C W, and Courville, C B Histologic Changes in the Brain in Cases of Fatal Injury to the Head VI Cyto-Architectonic Alterations, Arch Neurol & Psychiat **36** 1277 (Dec) 1936

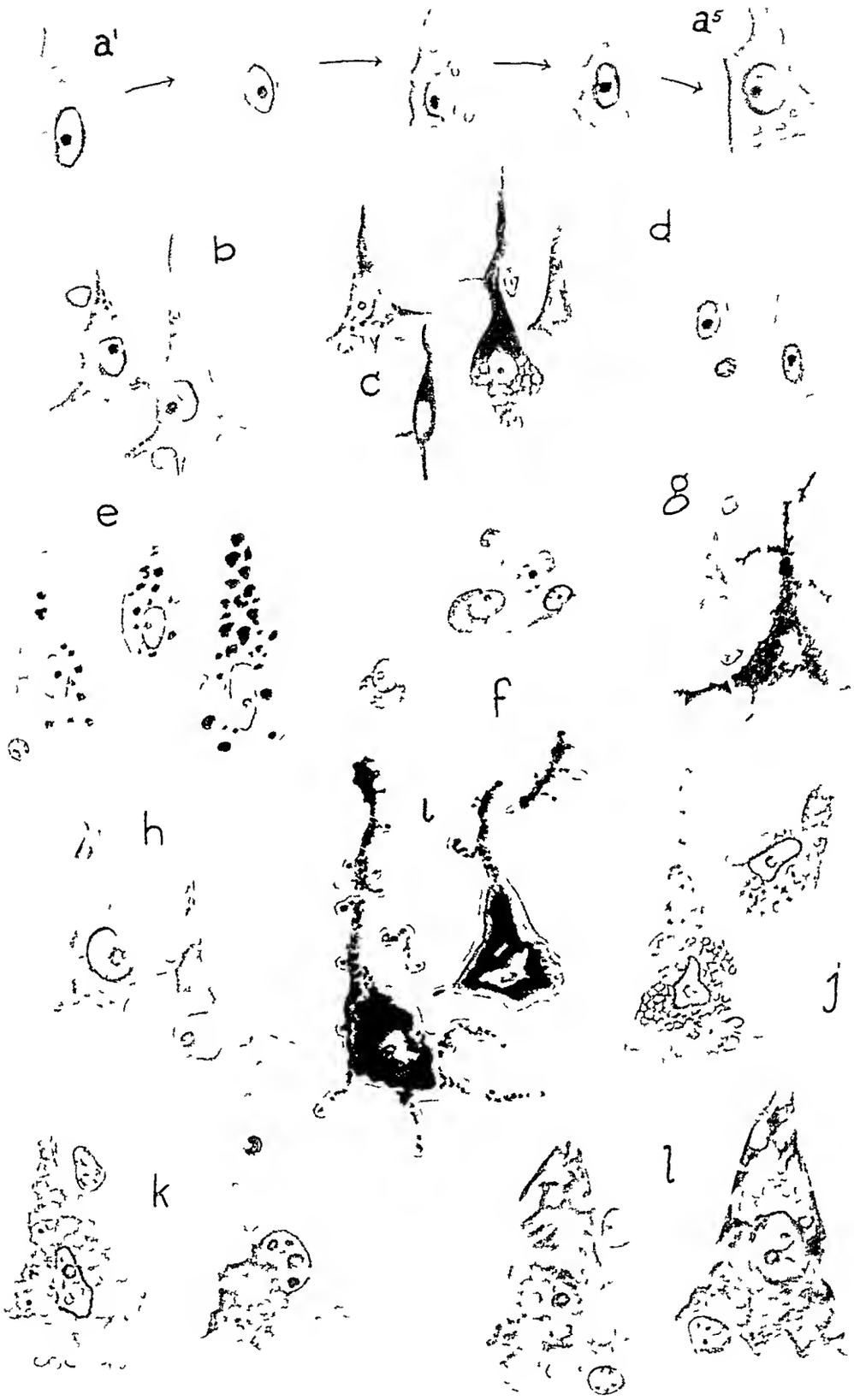

Fig 1.—Changes in nerve cells of the cerebral cortex incident to trauma. Here, a^1 to a^5 indicate progressive change leading to copper-colored cells, *b*, chromatolysis resulting from concussion, *c*, pyknosis, and, *d*, ischemic change, due to disturbances in circulation near contusions, *e*, pigmentary infiltration adjacent to cortical hemorrhage, *f*, pigmentary atrophy (fatty change), with example of multinucleation, *g*, preliminary and terminal stages of iron encrustation, and *h* to *l*, pronounced cell changes (traumatic degeneration), as shown in various preparations, (*h*, segmentation as a terminal stage of local edema [Bielschowsky-Plein method] *i*, coarse granulation of neurofibrils [Cajal method], *j*, cellular disintegration [phosphotungstic acid hematoxylin], *k*, "vacuolation" of nerve cells [hematoxylin and eosin, aniline blue], *l* condensation of chromatin [Bielschowsky-Plein method])

tions in the amount, appearance and distribution of certain chromatic granules found in the cytoplasm of the fixed nerve cell which have come to be known as Nissl substance, or tigroid granules Only on this basis can any order be made out of the confusing picture otherwise presented, confusing because the two types of changes are somewhat contradictory

The possible sources of error in interpreting general changes in nerve cells are manifold A common mistake is mistaking changes due to poor fixation of tissue which results in postmortem change for true pathologic alterations Nerve cells in particular are susceptible to improper fixation, and no doubt in the past many minor changes due to this cause have been interpreted as being due to disease We were fortunate in securing material that had been fixed by embalming within a few hours after death In most instances this had been done within three or four hours, and in only 5 of the 39 cases was embalming done more than five hours after death The longest interval between death and embalming was ten hours When the material was brought to the laboratory, it was promptly fixed in solution of formaldehyde U S P diluted 1 to 10[6]

One must be constantly on the alert to exclude preexisting disease in attempting to interpret one's observations Evidences of early parenchymatous syphilis led us to exclude 1 case of the series Alcoholism, so frequently the cause of the fatal accident, may also change the histologic picture In senile persons, who are so often run down by automobiles, the brain may show diffuse gliosis and alterations in nerve cells, such as sclerosis and lipoidal degeneration, which must not be confused with traumatic effects Focal areas of ischemia may be confused with minor contusions In persons who were comatose many hours before death, dehydration and lack of nutrition may play a part in producing generalized changes The influence of a high preterminal temperature (hyperthermia) or an elevation of temperature due to associated inflammatory lesions, such as bronchopneumonia, is to be considered Subclinical meningitis may produce meningeal and cortical changes, the cause of which may escape notice

While it may seem superfluous to mention it, there is a further danger in misinterpreting the normal variations in the cortical architecture, and even in cellular structure In some regions, relatively acellular areas may be mistaken for Verodungs by the uninitiated Normal variations in the cell, such as nucleolar vacuolation, must not be overemphasized Artefacts incident to or coincidental with the method of preparation may also be misleading at times

6 In order to assure ourselves that there were no chemicals in the embalming fluid which might interfere with or alter the staining or impregnating processes, an analysis of the fluid was made by the hospital chemist, Dr Albert Chaney No heavy metals or strong acids or bases were found to be present Some coloring material, possibly eosin, and an alkalizing substance, the nature of which was not determined, were present but did not seem to interfere with results obtained with the technical methods As evidence of proper fixation, we were able to obtain almost uniform success with the various metallic methods used Individual preparations which were not properly impregnated were discarded In case of doubt, normal tissues were run through at the same time to act as indicators to insure certainly of results

Changes in Cortical Nerve Cells Incident to the Shock of Injury (Commotio Cerebri, Concussion)—Perhaps the first observations as to the possible effects of the shock of injury on the cortical nerve cells of the brain were those of Budinger,[7] who noted that in cases of commotio cerebri there was a tendency for these elements to lose their capacity for staining with ammonia carmine At this early date, he presumed this change might be accounted for by the effects of *Gehirnerschütterung* Shortly thereafter, Scagliosi[8] investigated the problem by studying a series of changes in the brains of animals injured by being struck on the head with a hammer Within a short time after the injury, it was found that the tigroid substance began to undergo lysis in the vicinity of the nucleus, a process which progressively involved the rest of the cell until, at the end of twenty-four hours, the cell had lost its granular substance and had assumed a pale blue, homogeneous appearance Meanwhile, the cell process had undergone some hypertrophied varicosity and the formation of small club-shaped swellings at their terminations In repeating this experiment with dogs and monkeys, Jakob[9] found, after six days, widespread changes in the nerve cells (of the brain stem and even of the upper portion of the spinal cord, as well as of the cerebral cortex) in the form of swelling and intensification of the staining of the tigroid material, at times with early chromatolysis, eccentration of the nucleus and, occasionally, neuronophagia These alterations resembled the condition known as acute nerve cell disease described by Nissl, and it was assumed that the changes were reversible

Essentially the same alterations were reported by de Lisi,[10] who studied changes in the cerebral nerve cells in chickens and dogs According to this investigator, the changes were not constant but, when present, consisted in chromatolytic and

7 Budinger, K Ein Beitrag zu der Lehre von der Gehirnerschutterung, Deutsche Ztschr f Chir **41** 433-444, 1895

8 Scagliosi, G Ueber die Gehirnerschutterung und die daraus im Gehirn und Ruckenmark hervorgerufen histologische Veranderungen, Virchows Arch f path Anat **152** 487, 1898

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10 de Lisi, L Sulle alterazioni del sistema nervoso centrale degli animali, sottoposti a commozione cerebrale, Atti d Cong d Soc ital di neurol **4** 169-174, 1914

nuclear alterations, which (in agreement with Jakob) involved the cells in the brain stem and the upper portion of the spinal cord, as well as the cerebral cortex De Lisi stated the belief that these effects were due either to the shock of the injury or to some vasomotor effect (constriction) resulting therefrom

This study by de Lisi is of interest, for there has been a recent tendency to compare these effects of electric shock with those of concussion (Hassin [11]) Approaching the problem from a slightly different angle, Langworthy [12] studied the changes in the cortical ganglion cells after electric shock In cases of severe injuries, with immediate death, he found that the nuclei were shrunken and that they stained deeply, so that the chromatin threads and nucleolus could no longer be distinguished With less severe injuries the cell body was observed to be shrunken, with corresponding enlargement of the perivascular space There was a decrease in the amount of Nissl's substance, which appeared flaky and coarsely granular The cytoplasm stained a uniform deep color In a study of a series of these cases, it was found that the tigroid substance gradually reformed, being first restored either in the periphery of the cell or in the zone about the nucleus

In their experimental studies on the effects of explosions, Mairet and Durante [13] found that the nerve cells seemed unaltered as an immediate effect but that after five to nine months some atrophic changes in motor nerve cells were noticed, together with an alteration in the normal columnar arrangement of such cells Their observations seem to indicate that there is a fundamental difference between the effects of concussion due to head injury and those due to explosions

Osnato and Giliberti [14] noted an unevenness of the staining qualities of the pyramidal nerve cells of the cortex and the Purkinje cells of the cerebellum after injuries to the human brain and found considerable loss of tigroid material, especially in the latter elements Ramon y Cajal [15] had observed that experimental commotio cerebri resulted in "certain nutritive disorders" of the nerve cells in the form of such alterations as vacuolation and chromatolysis Neuburger [16] observed changes in the nerve cells (ischemic change) of the hippocampus in cases of gunshot wound of the brain and some alterations in the cells of the cerebellar cortex as well He attributed these widespread variations, however, to circulatory effects and not to the direct effects of injury Minkowski [17] concluded that the generalized chromatolysis and changes in the nucleus and protoplasm which are found after injury, which were described by previous observers and verified by him are to be accounted for on the basis of commotio cerebri

Dissatisfied with the conclusion that the changes described by previous investigators were the effect of "pure" concussion, Windle, Groat and Fox [18] and Groat, Windle and Magoun [19] repeated the classic experiments on guinea pigs and monkeys They found chromatolysis of the nerve cells of the vestibular nuclei and of the reticular formation of the brain stem and shrinkage of some of the large cortical (precentral) pyramidal cells (or sclerotic change) It is obvious that these investigators have only segregated the minor alterations in transitory states from more enduring ones and have further contributed to the highly artificial conception of concussion as a purely momentary clinical state

In our studies in the cases of injury to the human brain, a number of general changes were observed which might well be considered as manifestations of commotio cerebri, agreeing as they do with the experimental observations already cited In addition to chromatolysis, which seemed to be the most common change noted, other alterations in the nucleus, particularly in the chromatin material, have been observed

11 Hassin, G B General Pathological Considerations in Brain Injury, in Brock, S Injuries of Skull, Brain and Spinal Cord, ed 2, Baltimore, Williams & Wilkins Company, 1943

12 Langworthy, O R Histological Changes in Nerve Cells Following Injury, Bull Johns Hopkins Hosp **47** 11 (July) 1930

13 Mairet, A, and Durante, G Contribution a l'etude experimentale de lesions commotionelles, Rev neurol **35** 97 (Feb) 1919

14 Osnato, M, and Giliberti, V Postconcussion Neurosis Traumatic Encephalitis A Conception of Postconcussion Phenomena, Arch Neurol & Psychiat **18** 181 (Aug) 1927

15 Ramon y Cajal, S Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vol 2, pp 631-713

16 Neuburger, K Akute Ammonshornveranderungen nach frischen Hirnschussverletzungen, Krankheitforsch **7** 219 (June) 1929

17 Minkowski, M Klinisches und pathologisch-anatomisches zur Frage der traumatischen Hirnschadigung und ihrer Folgezustande, Schweiz med Wchnschr **60** 701 (July 26) 1930

18 Windle, W F, Groat, R A, and Fox, C A Experimental Structural Alterations in the Brain During and After Concussion, Surg, Gynec & Obst **79** 561 (Dec) 1944

19 Groat, R A, Windle, W F, and Magoun, H W Functional and Structural Changes in the Monkey's Brain During and After Concussion, J Neurosurg **2** 26 (Jan) 1945

Chromatolysis This condition, which has been consistently reported as one of the general changes in the nerve cells as a result of trauma to the head, has also been observed by us in our study of the effects of injury on the human brain [20] In a case in which the person had been killed outright, no change was observed in the amount, character or distribution of the tigroid substance In another case, with a survival period of about an hour, the tigroid substance was coarsely granular After one and a half hours, however, this substance was found to be absent in a ring about the nucleus in some of the cells, a change which was still more marked at the end of two and a half hours No further change was noticed after twelve hours, but

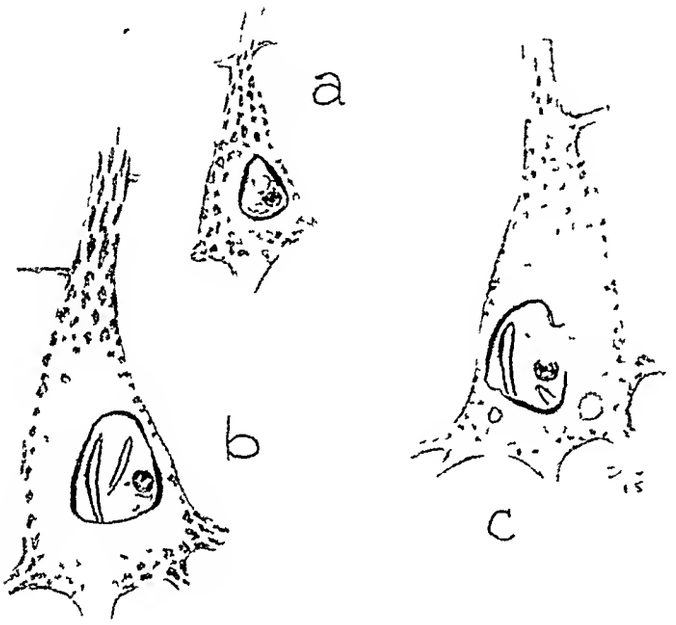

Fig 2—Chromatolysis incident to commotio cerebri (concussion), showing (*a*) early perinuclear loss of tigroid substance, (*b*) persisting ring of Nissl granules, with nuclear eccentration and distortion and folds in the nuclear membrane, and (*c*) agranular cell with vacuolation of the cytoplasm and nucleus (edema) and rupture of the nuclear membrane

after twenty-four hours (in a case with a survival period of thirty-one hours) the cortical ganglion cells were generally agranular, in the remaining few cells which contained this material it was irregularly distributed (fig 2) This was also true in 2 cases with survival periods of three and a quarter and three and one-half days At the end of six days, however, some cells were found which showed only a perinuclear loss of chromatic substance, an observation which indicates that there is some variability in the rapidity and extent of loss of tigroid substance This variability is likely dependent on the degree of shock of the original injury, on the character and degree of other traumatic effects and on what occurs in the interval between the injury and the time of death After fourteen days little granulation of the cells was found to be present, and after twenty-one and thirty-nine days' survival practically all the cells remained agranular

There are some alterations in the Nissl substance which have been described in cases of experimental cranial injury which we have not been able to verify in the human specimens which we have studied For example, de Luzenberger [21] described the collection of tigroid material at one pole of the cell after striking animals repeatedly on the head with a hammer This was most evident in the region of the injury and should perhaps be considered as a more local rather than a general effect Ingvar [22] described a similar and more general change in the nerve cells after centrifugation of the head and brain These specific types of alteration have been accounted for on the basis of a difference in the specific gravity of the tigroid substance (whatever be the true nature of this material) and that of the cytoplasm of the cell in general While certain theoretic situations affecting the head of man in the process of injury might be postulated, we have not been able to establish the presence of such alterations in the specimens which have come to our attention

On the basis of these observations in cases of injury to the human brain, one may conclude that the shock of severe injury is manifested within two hours by a loss of tigroid material, which loss is first evident in the perinuclear zone This process seems to proceed fairly rapidly, for after twelve hours it is widely present and after twenty-four hours one may find most of the cells affected by loss of this granular substance However, even after several days, perhaps in persons who have not been so seri-

20 It is aside from the purpose of discussion in this connection to go into the various arguments which have been advanced as to the nature, or even the reality, of this substance, which has been variously known as Nissl or tigroid bodies and chromophil or chromidial substance Contrary to the opinion of some investigators, it has been demonstrated in the living anterior horn cell of man But in general it is not found in the state of granulation in most circumstances, and it has therefore been assumed to be the coagulation product of fixation, in which certain other iron-containing granular elements of protein character are precipitated Be all this as it may, its uniform presence in normal circumstances and its dissolution under many pathologic conditions give one something to conjure with in the interpretation of neuropathologic states, even though the results fall far short of the original high hopes that its discoverer, Nissl, had for it

21 de Luzenberger, A Su d'una speciale alterazione delle cellule gangliari prodotta da trauma, Neurol Centralbl **17** 363, 1898

22 Ingvar, S Centrifugation of the Nervous System An Investigation of Cellular Changes in Commotion, Arch Neurol & Psychiat **10** 267 (Aug) 1923

ously injured but who have died of some intercurrent cause, granulation may still be present in many individual nerve cells In the cases with longer survival period (two weeks and more), granulation is poorly represented, if present at all This may indicate that reversal of this change may take place very slowly or that other factors, such as intercurrent infection (meningitis, pneumonia) or occurrence of interval hemorrhages, may act to continue the process which the original shock of injury has begun While one must be cautious in interpreting alterations in the tigroid material (since so many possible disturbing factors are present in these cases of human injury), a study of this material seems to verify the experimental observation of loss of this substance as a general effect of cranial injury

Alterations in the Neurofibrils This feature has not been noted as a general thing in the reported studies on experimental injury Therefore, there is nothing with which to compare our observations in cases of human injury This phase of the subject (commotio cerebri) was entirely ignored by Cajal, whose monumental studies on neurofibrillar reactions to local injury are of great help in the interpretation of injuries of the human brain From our studies, true alterations of the intracellular neurofibrils of nerve cells in general, as demonstrated by the Bielschowsky method, are limited in degree In 1 case after twelve hours some tortuosity and occasional fragmentation of these elements were observed, but after fourteen days no evidence was seen of any alteration of neurofibrils in nerve cells distant from the local injury With the use of reduced silver, however, an entirely different picture is presented, which has led us to conclude that the structures demonstrated by these two methods are not identical [23] Even in the cortex of persons killed outright some granulation of these elements were made out, a change which became increasingly apparent within the first few hours after craniocerebral trauma In this respect, the small pyramidal cells seemed to suffer from the effects of shock more than the medium-sized or large ones The character of the changes observed suggested that the neurofibrils underwent a process of coarse or fine granulation as an immediate effect if the shock was severe (persons with short survival periods), while with less severe injuries a slower process of change was noted—varicosities and fusiform enlargements were observed, apparently as preliminary changes leading to segmentation and coarse and fine granulation of these structures These alterations were found as late as twenty-one days after severe injury to the head an observation which suggests that they may be of the nature of a change which permits reversible reaction, but just how long this reaction may be delayed has not been determined

On the basis of these observations, it may be concluded that some alterations in the neurofibrils occur as a general effect of cranial trauma But since the Bielschowsky method shows relatively few structural changes, it may also be concluded that the reduced silver method demonstrates only some portion of these elements perhaps only a thin envelope, rather than the essential element of the fibril, whatever its nature and function may be How long these alterations persist in the injured cell is not known but it is clear that such changes are not incompatible with a living cell and are very likely reversible in character

Nuclear Changes These changes, while not marked or perhaps of great importance are nevertheless interesting Whether vacuolar changes in the nucleus and nucleolus are to be considered as evidence of edema or of some other regressive process is not entirely clear, but they will be described in connection with other alterations which are suggestive of edema Within two hours after severe injury to the head the nuclei of the cortical nerve cells may assume an eccentric position in the cell, their contours become irregular, and folds in the nuclear membrane are found, which suggest some degree of shrinkage of this structure This membrane may also show considerable variation in its thickness With longer survival periods, the nucleolus also becomes eccentric and may be found lying against the nuclear

23 Since the majority of sections studied for possible alterations in nerve cells were prepared by both the Bielschowsky and the Cajal method for neurofibrils, we have had opportunity to compare the two pictures resulting therefrom It soon became obvious that the two methods were demonstrating different parts or elements of the neurofibrils What appeared to be a perfectly normal neurofibrillar apparatus with the Bielschowsky method disclosed many and varied alterations with reduced silver It has therefore been assumed that the Bielschowsky method gives one a better impression of the functional state of the cell However, the consistent picture of the reduced silver method of Cajal must have some structural significance, even though we are unable to translate these appearances into physiologic counterparts It appears that the reduced silver method may demonstrate a fine sheath of the individual neurofibrils, one which is sensitive to pathologic change The Bielschowsky method, on the other hand, discloses the true element, which is much more resistant to abnormal processes That there may be some other, and more correct, interpretation of the phenomena is well recognized

membrane Of much greater interest are the changes in the contained chromatin material

Alterations in Chromatin Material These changes occur as a rather unusual general effect of cranial injury In normal circumstances the chromatin of the nucleus of a nerve cell is rather finely divided and fairly evenly distributed Within an hour or two after injury the chromatin material is found to be arranged in chainlike strands, and after twenty-four hours it is found to have assumed a coarser quality, forming either maplike patterns or agglutinations adherent to the nuclear membrane It is not until about two weeks have elapsed that certain bizarre arrangements of this material are to be observed While such alterations are developing this structure The significance of this change as a response to injury is not known

Other General Changes Other alterations in the cortical nerve cells seem to be incidental and are perhaps due to some undetermined local effect not otherwise evident Among the occasional observations in cases of human injuries have been described focal vascular lesions with ischemic change in the nerve cells of the hippocampus (Neuburger [16]) as a consequence of gunshot wounds of the brain We have noted occasional neuronophagia, irregularities in cell contour, rupture of the nuclear membrane and pyknotic change

Alterations in the Purkinje Cells of the Cerebellum.—Evidently to be accounted for only as

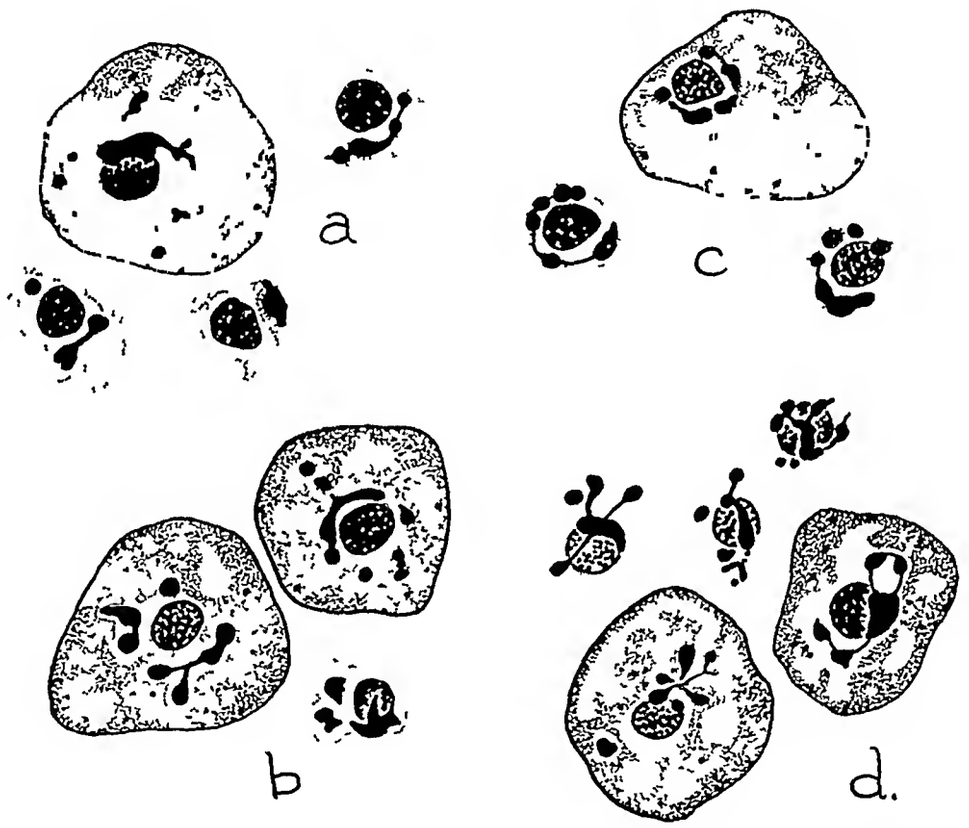

Fig 3.—Peculiar condensations of nuclear chromatin incident to commotio cerebri (concussion), showing (*a*) agglutination masses, (*b*) ring forms, (*c*) multiple masses and (*d*) mass-fibril combination patterns

found in the vicinity of local traumatic lesions, they also occur apparently as a general change in these circumstances Such changes persist for as long as thirty-nine days, but how much longer is not known Some of the interesting forms found after the aforementioned interval are shown in figure 3 The individual masses, of various sizes and shapes, may form a ring about the nucleolus, often forming a border to a perinuclear vacuole under these conditions In other cells, the various individual masses may be connected through elongated masses of this substance or through the medium of chromatin threads These patterns are usually found in the vicinity of the nucleolus often entirely en-

a general effect of trauma (commotio cerebri) are certain alterations in the Purkinje cells of the cerebellum, which are perhaps best described separately, although the individual changes are not greatly different in character from those previously described as being found in the pyramidal cells of the cerebral cortex Somewhat paradoxic in their behavior are these cells (which Cajal [15] described as showing most energetic and prompt reaction to local injuries) for they are rather easily affected by most noxious processes This is also true of their response to concussive effects Within an hour after severe cranial injuries the tigroid substance in some of these elements may be almost completely absent In 1 case with a survival

period of sixteen hours, the tigroid material was largely dissolved, and after thirty-one hours what little substance was still present was found in the upper pole or at the periphery of the cell After forty-eight hours the cells were completely agranular and remained so for an undetermined length of time

The neurofibrillar elements, demonstrated by the reduced silver method, were also definitely affected These elements may be found to be deficient, either in the peripheral (hirudiform change) or the central portion of the cell, or the entire structure may be coarsely or finely granular The presence of normal structures as demonstrated by the Bielschowsky method, while reduced to granulations as shown by the reduced silver method, is further evidence of the fact that these two methods demonstrate different structures

It may be concluded, therefore, that in man the Purkinje cells of the cerebellum reflect the general effects of trauma in much the same manner as do the pyramidal cells of the cerebral cortex These changes, too, are probably reversible and represent a transitory physical state the physiologic equivalents of which have as yet not been determined

Summary.—From the results of a number of reported experimental investigations, it has been shown that a generalized chromatolysis of the cortical ganglion cells is the usual response to cranial injury It has been assumed that this reaction is due to the shocking effects of the injury (Minkowski) and that these alterations probably correspond with clinical manifestations which have come to be known as concussion, or commotio cerebri It is of interest to know that we have noted similar changes in cases of injury to the human brain, as well as alterations in that portion of the neurofibrillar apparatus demonstrated by the reduced silver method, together with changes in the nucleus (irregularities in contour, folds in the nuclear membrane, eccentration of the nucleus and nucleolus and alterations in the size of the chromatin particles, as well as in their arrangement)

While all this is true, some details of the problem are not entirely clear In the first place, the brains studied in this investigation were from persons who succumbed to the effects of their injuries within a relatively short time Certainly the condition in patients who die within a few days does not represent the situation present in persons who suffer a momentary loss of consciousness after cranial injury Among the patients with longer survival periods, however, there are some who doubtless represent the group of patients with moderate injuries and who frequently recover Even in this group the changes here outlined were present Such alterations may therefore be considered as basic for at least moderate injuries

But the period of unconsciousness in the latter group was often relatively short, and complete recovery from any general symptoms would have been expected had not complications arisen Therefore, one should not attempt to account for temporary loss of consciousness, with restoration to the normal state in that respect within a few hours, on the basis of alterations in the nerve cells which persist for at least a month, or over In short, there is as yet no exact parallel in man between the generalized alteration in nerve cells and the relatively acute aspects of concussion But there is a possible basis for understanding certain of the subacute disturbances in the function of the central nervous system, especially in the psychic realm, which tend to clear up within a few months Therefore, one must be at least hesitant in describing all untoward subjective symptoms which follow "concussion" as purely functional in character

Changes in Nerve Cells Incident to Traumatic Cerebral Edema.—While the condition known as traumatic cerebral edema has been known for a long time, it has been only recently that any information has been available as to the possible changes in nerve cells that might follow the development of this state In fact, present opinions on the subject are the result of the merger of three separate lines of histologic investigation Over half a century ago, Macpherson [24] noted vacuoles in the cortical nerve cells after injury to the human brain, which he concluded to be the result of concussion He expressed the belief, further, that these vacuoles were the direct result of some vascular state which affected the nutrition of the cells and which resulted in a breaking down of the albuminous substance into fat While a definite effect on the physiologic state of the cell was assumed, the vacuole itself was not considered to be of fluid nature and was not thought of in relation to traumatic edema of the brain Since that time, vacuolation of nerve cells has been reported in cases of experimental injury, usually produced as the result of direct force, in which cerebral edema is a minimal condition Moreover, these vacuolated cells were evidently a local and not a generalized response (Scagliosi [8] and others) While such vacuolation has frequently been re

24 Macpherson, J Vacuolation of Nerve-Cell Nuclei in the Cortex in Two Cases of Cerebral Concussion, Lancet **1** 1127 (May 21) 1892

ferred to by subsequent investigators, the possible significance of this somewhat isolated observation made in cases of injury to the human brain has been generally overlooked Cajal [15] mentioned the possibility that vacuolation of nerve cells might be the result of commotio cerebri, as well as a general effect

Meanwhile, attention was directed to a type of cell change which was considered to be associated with certain circulatory changes (*Wasserveranderung* [Nissl], *odematose Ganglienzellveranderung* [Jakob]) This type of cell change was found as an agonal effect or with extreme cerebral edema ("wet brain"), such as might follow heart failure It was also noted at the cells did occur, these elements were rather resistant to the influence of excess fluid in the nerve tissue These observations were verified by Ferraro,[26] who was able to demonstrate the presence of large vacuoles in the cortex of hydrated rabbits, establishing beyond any question the fact of edematous change as a possibility in the presence of increased amounts of fluid in the tissue of the brain Reid [27] demonstrated similar changes in nerve cells with this method, accentuating the degree of cellular vacuolation by removing the skull cap and opening the dura of his experimental animals before injecting the hypotonic solution These various degrees of alteration are due to edema (fig 4)

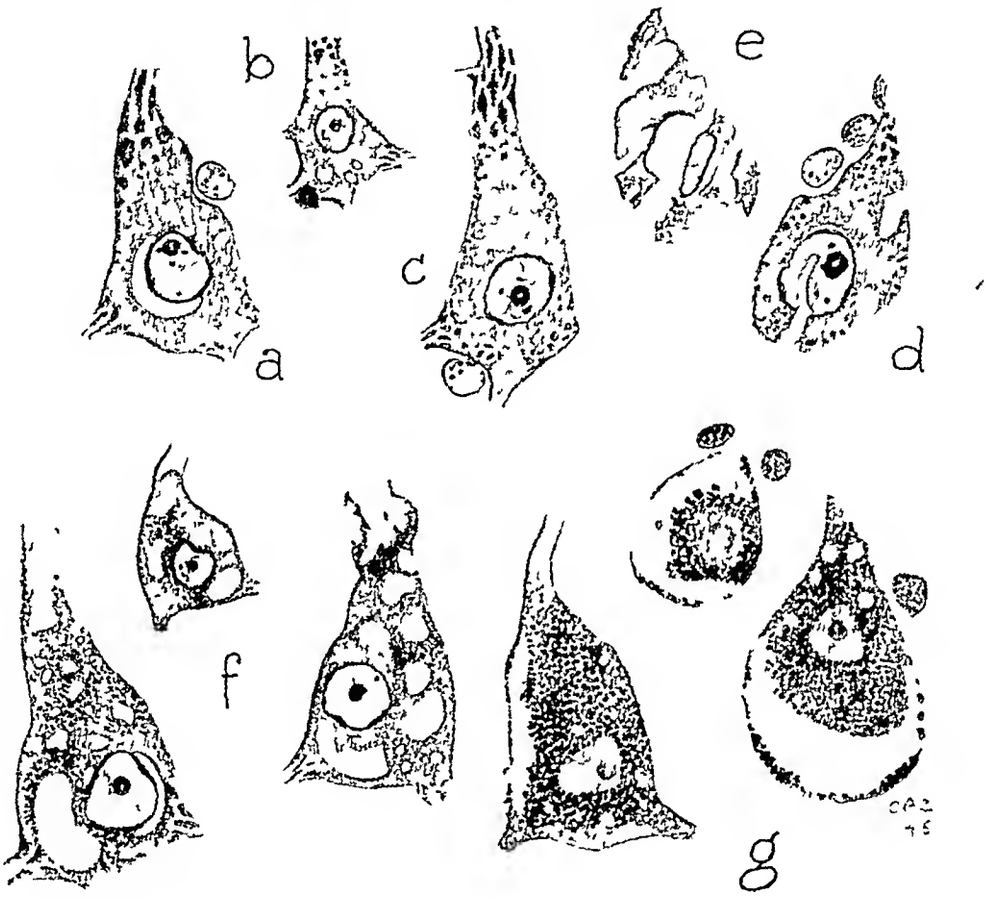

Fig 4—Cellular alteration incident to traumatic cerebral edema Here, *a* to *e* indicate changes seen after injury to the human brain (*a* to *c*, general changes, *d* and *e* changes about local traumatic lesions), *f* and *g*, changes after experimental hydration of the brain (*f*, cellular vacuolation [after Ferraro [26]], *g*, formation of cellular fluid lakes after removal of the skull and dura [after Reid [27]])

margin of such vascular lesions as hemorrhage or infarction

The third line of investigation which was to show that this type of cell change might also be found as a traumatic effect was introduced by Weed,[25] who studied the effects on the brain of intravenous injection of hypotonic solutions in experimental animals This investigator observed that while vacuolar changes in the nerve

The fact that vacuolation of nerve cells takes place as a consequence of cranial trauma (Macpherson), the occurrence of edematous change as a special type of change in nerve cells (Nissl, Jakob) and the association of this change with hydration of the brain, therefore, established the possibility that vacuolation as a type of change in nerve cells might well occur as a consequence

25 Weed, L H The Effects of Hypotonic Solutions upon the Cell-Morphology of the Choroid Plexuses and Central Nervous System, Am J Anat **32** 253 (Sept) 1923

26 Ferraro, A The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, J Nerv & Ment Dis **71** 129 (Feb) 1930

27 Reid, W L Cerebral Oedema, Australian & New Zealand J Surg **13** 11 (July) 1943

of traumatic cerebral edema Since the nerve cells were found to be resistant to the effects of an excess of fluids in the nerve tissues (Weed [25]) in cases of traumatic cerebral edema of the generalized type (Courville [28]), it was to be expected that such alterations would be of minor character, a conclusion shared by Reid,[27] and would occur in the form of vacuoles which were filled with fluid [29]

In our investigation of the general effects of injury to the human brain, vacuolation of nerve cells, not otherwise accounted for, was observed within an hour or two after injury These vacuoles were first noted in the nucleus and the nucleolus The nuclear vacuoles, at first small, increased in prominence with the lapse of time, until the occurrence of multiple vacuolar spaces resulted in a maplike design in the nuclear chromatin The vacuoles in the nucleolus were usually small and droplike, at times two or three being found in this structure

After twenty-four hours, in cases of definite cerebral edema, one may find small, semilunar clear spaces about the nucleus (perinuclear vacuoles) These may be overlooked unless carefully sought for in routine preparations By this time, however, the pericellular and perivascular spaces may be notably enlarged, suggesting an excess accumulation of fluid in the brain and thus leading one to search for these more specific alterations incident to a disturbance of fluid balance within the cell Such changes have been observed in typical conditions after three and a half days Vacuoles in the cytoplasm do not appear as a rule and, if present, tend to occur after several days have elapsed They may be found as long as several weeks after the injury These cytoplasmic vacuoles are small and sharply defined and usually occur in the basilar portion of the cell, in the region of the nucleus

"Edematous Change" and Alterations in Nerve Cells Associated with Cerebral Edema Nerve cells showing edematous change are slightly smaller than normal and contain a shrunken irregular, hyperchromatic nucleus, they have no typical tigroid granules but show irregular masses of chromatic material, which stains deeply On the other hand, the nerve cells which contain the vacuolar spaces aforementioned are pale and agranular, and their nuclei, likewise, are somewhat lighter in color, owing to the presence of nuclear vacuoles which scatter the granular material Therefore, the changes in nerve cells incident to cerebral edema are not entirely synonymous with the "edematous change of nerve cells" As has already been shown, there are two factors at work in the production of these generalized changes—the shock of the injury (commotio cerebri) and a disturbance in tissue fluid balance The end product of these two processes is the cell change previously described, resulting in an agranular, pale cell in which the nucleus is shrunken and eccentric and fluid vacuoles are sometimes found, both in its cytoplasm and in its nucleus

Summary—The nerve cells of the cerebral and the cerebellar cortex may be generally affected as a result of injury, in contrast to certain other alterations which occur in response to a local traumatic lesion As has just been indicated, these changes consist of a combination of two effects—that of shock of injury, which produces unconsciousness, and a disturbance in the fluid balance in the cerebral tissues, which has come to be known as traumatic cerebral edema The end result, so far as the changes in the nerve cells are concerned, is dependent on the relative effects of these two processes The shocking effect of the injury appears to be responsible for loss of the tigroid substance from the cell, a process which begins usually in the perinuclear region, granulation of that part of the neurofibrillar structure demonstrated by the reduced silver method, shrinkage of the nucleus, with assumption of an irregular shape and the formation of folds in the nuclear membrane, and, ultimately, peculiar agglutination and pattern formation of the chromatin substance These changes are evidently reversible, at least in their minor stages The cell changes are probably to be found long after the patient has recovered consciousness, so they cannot be said to be responsible for the acute manifestations of concussion While there is no known way in which the physiologic counterpart of these structural changes can be evaluated clinically, it is possible that they may account for certain of the psychic alterations which so often occur after commotio cerebri At any rate, they furnish some reason for caution in describing all such manifestations as being purely functional in character

CHANGES IN NERVE CELLS DUE TO LOCAL POST-TRAUMATIC LESIONS

Local traumatic lesions which might be responsible for change in nerve cells may be divided into two categories (1) lesions causing pressure on some region of the cerebral cortex such as depressed fracture or extradural and subdural hemorrhage, and (2) lesions causing destruction of the cortical substance proper, such as contusion and laceration of the cortex Because the

28 Courville, C B Structural Changes in the Brain Consequent to Traumatic Disturbance of Intracranial Fluid Balance, Bull Los Angeles Neurol Soc 7 55 (June) 1942

29 Courville, C B Pathology of the Central Nervous System, ed 2, Mountain View, Calif, Pacific Press, 1945

experimental observations in cases of these two types of lesions have been recorded separately, and because from a clinical standpoint the two situations are quite distinct, it has seemed advisable to consider each as an individual entity

Compressive Lesions—Under this heading will be considered only those lesions which cause pressure on the cerebral cortex without producing actual structural disorganization or damage Thus, if a depressed fracture results in laceration of the underlying cortex, one is dealing with something else than compression This distinction is important, for without physical damage one has reason to believe that changes in the nerve cells which might be due to the compression are reversible

Destructive Lesions—A different situation exists so far as contusions and lacerations are concerned Within the area of destruction it may be assumed that all parenchymatous and interstitial elements are alike destroyed Moreover, at the margin of the lesion there occurs a zone of destruction in which the elements are immediately killed, although their disintegration may be delayed for some time, owing to "preservation," a process which will subsequently be described This zone of disintegration may widen to some extent as time goes on, but in case of contusion there soon becomes apparent a fairly sharp margin to the lesion In lacerations, however, the margin between the preserved tissue and the zone of destruction is not so sharply drawn, and pockets of nerve tissue may continue to undergo dissolution for a considerable interval of time Adjacent to the zone of destruction is a second zone, in which the elements may sustain physical damage and yet survive in a crippled or "mummified" state for a considerable interval of time Still more distal is a zone of reversible reaction in which the nerve cells, as well as other elements, are not so seriously injured but that they can be restored to normal structure, and perhaps to normal function

Since alterations due to compression are the least important and, by deduction, the least evident, these changes will be considered first Such alterations are evidently reversible in character, in contrast to the destructive, or necrobiotic, changes which are to be expected in case of contusions or lacerations

CHANGES IN CORTICAL NERVE CELLS DUE TO LOCAL COMPRESSION

Most of what is known about the effect of local compression on the cortical nerve cells has been learned from experimental studies on animals This is an obvious necessity, since the majority of human patients with local compression after injury do not succumb to the lesion Apparently, in those instances in which death has taken place from some associated lesion a critical pathologic study of changes in nerve cells under the compressing lesion has not been made In the early days of experimental histologic examination this subject seemed to be rather popular and one finds that a number of notables investigated the question experimentally — von Bergmann, Adamkiewicz, Albert, Ziegler and Kahler Some of their studies, however, were directed toward alterations in the spinal cord rather than in the brain One of the first critical studies was that of Neumayer,[30] who studied the changes in the cortex of rabbits after compression incident to a lead plate introduced between the cranial vault and the dura This investigator divided the changes that followed into four periods (1) In the first period (six to thirteen hours) no degenerative changes were found, although there was loss of the chromatic material in the cytoplasm of the nerve cell, (2) in the second period (after twenty-four hours) degenerative changes became apparent in the nerve fibers of the tangential fiber layer, as well as in the layer of the small pyramidal cells, (3) in the third period (two to ten days) proliferation of the interstitial elements "at the expense of the nerve cells" was observed, while (4) in the fourth period (ten to sixty days) a progressive disintegration of the nerve elements was noted

Roncali[31] repeated this work on dogs, and he, too, classified the changes observed into four periods After twenty-four hours, he observed that there was an initial degeneration of the nerve cells and fibers of the superficial layers of the cortex, with deformation and decoloration of the nerve cells Up to five days, changes in the nerve cells, from minor chromatolytic alterations up to complete destruction, were found in the molecular layer and the superficial and middle layers of Golgi From ten to fifteen days, alterations in the nerve cells of all layers and to all degrees were in evidence After twenty days, disintegration of the nerve elements was progressive

In what is perhaps one of the first studies on the effects of pressure on the cortex in cases of extradural and subdural hematoma, Ewing[32] found that beneath the area of pressure the nerve cells had lost their tigroid substance in whole or in part, the loss being first evident in the perinuclear zone and the peripheral zone being the last to show traces of them Essentially the

30 Neumayer, L Die histologischen Veranderungen der Grosshirnrinde bei localem Druck (Experimentalstudie aus dem histologischen Laboratorium des pathologischen Institutes zu Munchen), Deutsche Ztschr f Nervenh **8** 167, 1895-1896

31 Roncali, D B Intorne alle alterazioni nella fina tessitura dell' sostanza nervosa dell' encefalo conseceture delle compressione sperimentale, Arch ed atti d Soc ital di chir **12** 144, 1898

32 Ewing, J Studies on Ganglion Cells, Arch Neurol & Psychopath **1**.1, 1899

same changes were recorded in a case of recent extradural hemorrhage, as well as in 3 cases of chronic subdural hematoma

With the aid of his reduced silver method, Cajal[15] studied the effects of compression on the cortical nerve cells in experimental animals In addition to chromatolytic changes and some degree of vacuolation, he observed after six hours of cerebral compression what he designated as a "hypertrophic neurofibrillar state," manifested by local thickening and intense stainability of these elements This change was apparently only transitory, for it persisted no longer than two days A more typical change was a fusiform state of the fibrils, which became evident from ten to twenty-four hours after compression and also disappeared in two days A "state of discontinuous or granular reticulum" was also observed in his cases, a condition in which granulation of the somatic reticulum was observed It should be pointed out that these complex changes in the neurofibrillar structures were not typical of compression for they were also found in destructive lesions of the cortex We have observed similar changes in nerve cells of the human brain at the margins of contusions, as will shortly be described

A more recent experimental study on changes due to cortical compression is that of Ugurgieri[33] He found that in rabbits the chromatic substance showed the earliest changes with compression of the brain by a complex mechanism Neuronophagia was occasionally observed, as were sclerotic (pyknotic) changes, and at times atrophic alterations in the nerve cells These observations did little more than confirm those of earlier investigators

In this series of cases we have had little opportunity to study the alterations in nerve cells which might be considered to be due to pressure alone In 1 case of subdural hemorrhage the nerve cells beneath the hemorrhage were found to be agranular, the nucleus was eccentric in many cases, and dislocation of the nucleolus (eccentration) was also evident However, since similar changes were rather widespread, incident perhaps to commotio cerebri or an associated condition, one could not say with certainty that these cell changes were actually due to local pressure

In a case, not of this series, studied by one of us (C B C), a patient had sustained a local depressed fracture of the left parietal region of the skull An electroencephalogram had been made, and abnormal (slow) waves were found coming from the region of the depression The patient died of an intercurrent condition, and at autopsy no gross change in the cortex beneath the depression could be found A block of tissue was taken from this area and another (for comparison) from a corresponding area in the opposite parietal lobe The nerve cells in the cortex subjected to compression showed a notable loss of tigroid substance as compared with the normal cortex on the opposite side, minor nuclear alterations were also observed Whether these changes were to be accounted for by continued pressure or by a minor, but not evident, contusion at the moment of impact, as Naffziger and Glaser[34] averred, is of course debatable

In conclusion, one must state that local pressure on the cortex can produce minor, and in most instances reversible, changes in the affected nerve cells These changes consist in progressive loss of tigroid substance and eccentration of the nucleus If the pressure is of considerable degree (as has been demonstrated in the animal experiments), actual degenerative changes in the nerve cells may take place It may be that such changes are to be accounted for by an interference with their regional blood supply rather than by any mechanical effect of the pressure From a clinical standpoint, it is rather unlikely that such degrees of pressure occur with any frequency As Naffziger and Glaser[34] have shown experimentally, depressed fractures are not usually accompanied with any change in the cortex unless the cortex was bruised at the time of injury This observation we have been able to verify in man in the case of old depressed fractures, the underlying cortex proving normal in every discernible aspect While minor chromatolytic changes may occur in the nerve cells of the cortex compressed by extradural hemorrhage, subdural hemorrhage or hematoma, it is likely that a fatal issue ensues before destructive changes occur in these cells In man, therefore, as in experimental animals, a loss of tigroid substance (whatever may be the nature and significance of this material) with minor nuclear changes is about all that one can expect to find as a consequence of pressure on the cortex

NEURONAL CHANGES INCIDENT TO DESTRUCTIVE LESIONS OF THE CORTEX

The history of the study of changes in nerve cells as a result of local injury is now almost a century old, and yet there has been no known effort to survey these effects in any comprehensive way Virchow[35] seems to have been the

33 Ugurgieri, C Compressioni sperimentali del sistema nervoso centrale II Compressioni cerebrali lente e progressive, reperti isto-patologici, Riv di neurol **7** 113 (April) 1934

34 Naffziger, H C, and Glaser, M A Experimental Study of Effects of Depressed Fractures of the Skull, Surg Gynec & Obst **51** 17 (July) 1930

35 Virchow, R, 1857, cited by Dege-

first to make such observations, noting the occurrence of "calcified" ganglion cells at the margin of old traumatic lesions of the cerebral cortex Other observers also studied the cortical changes in wounds of the human brain (Tigges [36] Jolly,[37] Ceccherelli [38] and Popoff [39]) before the era of experimental investigation, which began in earnest about 1885 Oddly enough, these early experimental observations seemed to confirm the occurrence of nuclear division, a change which had been noted in cells at the margin of old cortical contusions, and one which had meanwhile been largely forgotten Aside from the repeatedly observed karyokinetic figures in nerve cells at the margin of experimental cerebral wounds, little else was noted as a specific change until de Luzenberger [21] performed his interesting experiments by striking animals on the head with a hammer As a result, he noted that the chromatin material (Nissl substance) in the nerve cells in the region of the blow had collected at one pole of the cell Hauser [40] studied the changes in nerve cells in the margin of contrecoup lesions at the base of the brain and reported fragmentation and granulation of these elements Bianchi [41] reported vacuolation, lipoidal degeneration and granulation of the neurofibrils at the margin of experimental injuries of the brain

It remained for Cajal [15] to make a critical experimental study of the various changes in nerve cells as the result of local injury With the use of his reduced silver method, he gave particular attention to the alterations in the neurofibrillar apparatus He did observe, however, the occurrence of vacuolation, chromatolysis and pyknosis (sclerotic change) He found that the cellular fibrils underwent coarse or fine granulation (followed by cell death within a few hours), hirudiform alteration (with cell death in from three to seven days) and fusiform change, in which the individual neurofibrils formed fusiform swellings, which seemed to be a prelude to granular degeneration He also noted that after two to four days the reticular apparatus of Golgi had undergone transformation It was not possible to demonstrate the apparatus in the nerve cells adjacent to the wound, but slightly distant from the margin of the wound it was found to be reduced to granulations Still more distant the apparatus was intact but in the form of large cordons and groups of loops and meshes

In a general review of the problems of the pathology of cerebral injury, Dege [42] noted something of the historical development of knowledge of the histopathology of such injuries and commented briefly on the various changes observed in the nerve cells and fibers, as well as in the other elements Among the various possibilities were mentioned "calcification," vacuolation, loss of granulation, atrophy, cell shrinkage and other regressive changes He reviewed in some detail the observations of Ernest,[43] who was interested especially in the alterations in the Nissl substance after trauma, and those of Cajal, whose studies have already been mentioned This review by Dege seems to be the most comprehensive survey up to this time, although it is not very long

Since then a number of students of the problem of local cranial injury have made incidental observations on changes in nerve cells For example, Penfield [44] noted that the cortical ganglion cells in the vicinity of experimental puncture wounds underwent a slow process of chromatolysis, which was quite evident after five weeks and which persisted as long as seven months Staemmler [45] observed non-nucleated "ghost cells" about the margins of gunshot wounds of the cerebral cortex, as well as occasional instances of neuronophagia Winkelman and Eckel [46] noted the occurrence of ischemic changes and tortuosity

36 Tigges, W Pathologisch-anatomische und physiologische Untersuchungen zur Dementia paralytica progressiva, Allg Ztschr f Psychiat **20** 313, 1863

37 Jolly Ueber traumatische Encephalitis, in Stricker, S Studien aus dem Institut fur experimentelle Pathologie in Wien aus dem Jahre 1869, Vienna, W Braumuller, 1870

38 Ceccherelli, A Ein Beitrag zur Kenntnis der entzundlichen Veranderungen des Gehirns, Med Jahrb, 1874, pp 343-346

39 Popoff, L Ueber Veranderungen im Gehirn bei Abdominaltyphus und traumatischer Entzundung, Virchows Arch f path Anat **63**·421, 1875

40 Hauser, G Ueber einen Fall von Commotio cerebri, mit bemerkenswerthen Veranderungen im Gehirn, Deutsches Arch f klin Med **65** 433, 1900

41 Bianchi, V Alterazioni istologiche della corteccia cerebrale in seguito a focolai distruttivi ed a lesioni sperimentali, Ann di nevrol **30** 61 1912

42 Dege, A Die traumatischen Schadigungen der Nervenzellen, Nervenfasern und des Nervenstutzgewebes in Verletzungen des Gehirns, in von Bruns, P Neue deutsche Chirurgie, Stuttgart, F Enke, 1920, vol 18, pp 70-75

43 Ernest, P Das Nervensystem, in Aschoff, L Pathologische Anatomie, ed 3, Jena, G Fischer, 1913, vol 2, pp 343-428

44 Penfield, W Meningo-Cerebral Adhesions A Histological Study of the Results of Cerebral Incision and Cranioplasty, Surg, Gynec & Obst **39** 803 (Dec) 1924

45 Staemmler, M Ueber Veranderungen der kleinen Hirngefasse in apoplektischen und traumatischen Erweichungsherden und ihre Beziehungen zur traumatischen Spatapoplexie, Beitr z path Anat u z allg Path **78** 408, 1927

46 Winkelman, N W, and Eckel, J L Brain Trauma Histopathology During the Early Stages, Arch Neurol & Psychiat **31** 956 (May) 1934

of cell processes (pyknotic change) near foci of injury, which are now recognized to be the result of associated vascular change rather than an immediate effect of the injury Hassin [11] called attention to this fact, suggesting that some of these changes are due to cerebral edema and ischemia He described the alterations incident to acute traumatic degeneration, which, in the final analysis is about the most characteristic traumatic change in these cells

In describing the various changes in the cortical nerve cells as a consequence of local injury which we have encountered in the series of cases which form the basis of the present study, it has seemed advisable to describe all of the various alterations which have been encountered in the vicinity of contusions or lacerations of the cerebral cortex and then to try to evaluate their occurrence on the basis of the etiologic process which is most likely responsible for their presence It will soon become evident that the accompanying vascular changes play an important part in the production of these alterations and that the problem is not made any simpler by the fact that more than one change may be present in a single cell On this basis, the following alterations in these nerve cells will be described (1) preservation necrosis (Cajal), (2) alterations in the reticular apparatus of Golgi, (3) pigmentary infiltration, (4) pyknotic (sclerotic) change, (5) ischemic change, (6) pigmentary atrophy, (7) vacuolar change, (8) acute traumatic change, minor and major, (9) multinucleation, and (10) ferrugination ("calcification")

Preservation Necrosis of Cajal—As the result of his experience in studying the response of the brain to experimental trauma in the light of pictures produced by his reduced silver method, Cajal [15] was able to describe a peculiar type of reaction which he designated as preservation necrosis

> The least commotion, stretching or compression, especially when they are accompanied by diffusions of blood beyond the edges of the wound, bring about the almost instantaneous death of the nervous protoplasm and the peculiar phenomenon of *preservation,* that is, necrosis associated with the most perfect morphological integrity

This interesting type of reaction we have been able to note just as clearly in cases of injury to the human brain as Cajal and his co-workers did in their experimental animals If a block is taken from the cortex at the margin of a local contusion or in the vicinity of a small cortical hemorrhage and the individual sections are impregnated with silver by Cajal's reduced silver method, it will be found that the bodies of the nerve cells in the immediate proximity of the lesion, together with their axons and dendrites, are clearly demonstrated in all their details, these cells evidently have an unusual degree of affinity for the reduced silver Such elements appear much blacker than do the uninjured cells somewhat farther removed from the margin of the lesion This is an unusual situation, for, as Cajal has pointed out, these cells are dead elements, as is shown by their complete inability to react, as determined by following the changes manifested in a series of experimental animals Cajal accounted for this phenomenon as follows [15]

> This and other cases of maintenance of the morphology of the axon in consequence of hemorrhage show that, as we said in connection with the preserved fibers of the nerves and spinal cord, in the phenomenon of preservation a great part is played by some antiautolytic principle which proceeds from the sanguineous exudate and is fixed in the protoplasm of the axon

As a result of this reaction, the various elements of the cell are even better demonstrated than those of the living neurons in adjacent regions of the cortex, even though the cells so demonstrated are completely defunct In cases with longer survival period, the cells fail to show the typical response of living cells, with the formation of "buds balls or other neurofibrillar reactions peculiar to traumatized axons" Not only are the dendrites and axons clearly demonstrated, but under suitable conditions the body of the nerve cells adjacent to these focal lesions will be found to show this preservation necrosis The cells so affected will present a perfectly intact neurofibrillar apparatus and nucleus The nonmedullated dendrites and regional nerve fibers are likewise perfectly demonstrated Not all the cells at the margin of these wounds undergo this type of change, however, some of them give evidence of disintegration of the neurofibrils, nucleus and expansions It is assumed that such cells have not been affected by the antiautolytic principle and are therefore already beginning to present evidence of their death As Cajal has pointed out, unless one understands this fact, one may fall into considerable error in the interpretation of the histologic picture in the reduced silver preparations of tissue from the margins of lesions, even those of seven to ten days' standing This phenomenon of preservation accounts for the delayed disintegration and phagocytosis of many of the parenchymatous elements at the margins of contusions and lacerations during this early period

While this specific type of preservation necrosis is not peculiar to traumatic lesions (since it may be found in the region of cortical hemorrhages of any cause), it is characteristically ob-

served in such lesions as contusions or lacerations, which are invariably accompanied with some degree of effusion of blood

Alterations in the Golgi Apparatus.—While our human material was not suited to a study of traumatic alterations of the Golgi apparatus, it seems worth while to make a brief note of Cajal's observations,[15] especially since we have found that the cellular alterations in man parallel so closely those observed in experimental animals Cajal found that the reticular apparatus of Golgi was degenerated in the nerve cells in the margins of cerebral wounds of kittens or puppies killed from two to four days after the wound had been made The amount of the damage was dependent on the degree of commotion or contusion of the brain tissue produced at the time of the injury At the very edge of the wound, the reticular apparatus was completely degenerated Somewhat more removed from its margin, the reticulum was fragmented, granular and at times reduced to dust Still more remote from the wound, this structure had been converted into a series of loops and meshes, which was often found entirely on one side of the displaced nucleus Distal to this zone the reticular apparatus appeared entirely normal

These observations suggest that the cells adjacent to the margin of the wound were dead, for in dead cells the reticular apparatus disintegrates rapidly In the less damaged, and more distal cells the minor alterations in this structure were probably reversible, representing only the early stage of the process of change

Pigmentary Infiltration.—It has long been recognized that the nerve cells in the vicinity of hemorrhages often contain a brownish granular pigment This was once designated as "formalin pigment" and was thought to be due to the demonstration of some preexistent substance in the cell incident to fixation with solution of formaldehyde U S P No doubt such pigmentation of nerve cells has likewise been previously observed in the case of traumatic hemorrhage, although little seems to have been made of it Winkelman and Eckel[46] reported finding such pigment in the nerve cells in the vicinity of traumatic cortical hemorrhages, and we have frequently observed it in similar circumstances While it is not necessarily an exclusive traumatic change, it is of frequent occurrence in cases of contusion (in which hemorrhage is conspicuous), as well as in cases of cortical and subcortical traumatic hemorrhage Therefore a brief description of the change and something said about its possible significance will not be out of order

In the series of specimens which formed the basis of this study pigmentary infiltration of

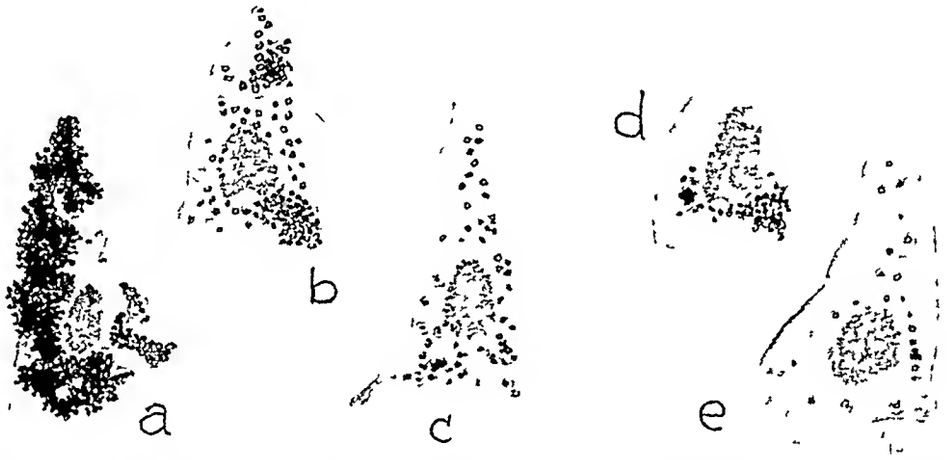

Fig 5.—Pigmentary infiltration in the vicinity of cortical hemorrhage (contusion), showing varying amounts of hematogenous pigment in (*a*) nerve cells immediately adjacent to the hemorrhage and (*b* to *e*) cells progressively removed from it (*c*, diffuse spread, and, *d*, localized collection of pigment in the cytoplasm) Survival period, six and three-fourth hours

nerve cells was found within a few hours after cranial injury and as long as three and a half days after such injury, always in the immediate vicinity of an effusion of blood into the cortex The amount of pigment was greatest in the cells in the immediate vicinity and decreased with the distance from the hemorrhage In the cells near the effusion the pigment granules were larger were round or oval and were frequently found in all portions of the cytoplasm, but not in the nucleus In these circumstances, the cellular details were sometimes entirely obscured by the mass of pigment In the cells somewhat removed from the contusion the injured pigment occurred in the form of fine grains and was found most often in the periphery of the cell or limited to one pole (fig 5) Since more pigment was found in the cases with longer survival periods it is suggested that the process must be a progressive one at least up to a certain point

Examination of the pigment granules with the aid of the higher powers of the microscope indicates that these granules very likely result from the agglutination of many small, powder-like grains of pigment material The larger grains often assumed an irregular and finely nodular shape, which further suggested such an origin These large nodules, somewhat darker than the fine grains found in the cells more removed from the margin of the hemorrhage, were also observed to have a lighter-colored center, similar in shade to that of the finer grains It may be that some action of the cellular cytoplasm agglutinates the pigment granules and imparts a darker color to them

Pigment of similar nature was also occasionally found in other cellular elements in the vicinity of the hemorrhage, suggesting that the pigment was hematogenous and came from disintegration of the red cells At times it was observed in some of the interstitial cells, chiefly the microglia elements, especially when they had assumed the characteristics of compound granular corpuscles In these cells the pigment granules were large, often irregular and almost black At times it appeared as though this pigment was also contained in astrocytes, although always in small quantities It was found in abundance in the endothelial cells of the regional capillaries

We are of the opinion that this pigment is hematogenous and is derived from red cells of the hemorrhagic effusion The reasons for this conclusion may be enumerated as follows (1) In the immediate vicinity of the hemorrhage fine grains of similar pigment may be found loose in the tissues, suggesting that it is derived from the hemorrhagic effusion, (2) the pigment is most abundant in the nerve cells in the immediate vicinity of the hemorrhage, becoming less and less evident with the distance of the cells from the margin, (3) the presence of the pigment in other elements, especially the regional macrophages and the endothelial cells of the small vessels, indicates that it is a substance of local origin, not due simply to formaldehyde fixation of the tissues, and (4) pigment-laden nerve cells are found only in the vicinity of such hemorrhages The very fine particles of hemoglobin which are released when the red blood cells disintegrate are apparently carried in suspension in the tissue fluids The small size of these grains permits them to be carried into the nerve cells in the course of interchange of cellular fluids, perhaps aided by the excess amount of fluid incident to edema Once in the cell, the cytoplasm acts to agglutinate the particles into larger granules, which soon become evident in the nerve cell, even under the lower powers of the microscope The suspension of such grains in the tissue fluids, thus accounting for their being carried into the cell, is also suggested by the fact that isolated granules in the cytoplasm of the cell are often observed to be surrounded by a small vacuole

The effect of such pigment on the nerve cell is conjectural We have found no evidence that it has any specific lethal effect on the host when present in small amounts While we have not chanced to observe it later than three and a half days after the injury, it may be present for a longer interval At the end of fourteen days, for instance, we have observed golden yellow inclusion particles in regional nerve cells, their presence suggesting that the pigment continues its process of disintegration within the nerve cell as it does outside, passing through the usual stages of coloration in the process While the pigment has been observed in "ghost cells" in the vicinity of local traumatic cortical lesions (sometimes the outline of the cell is clearly delineated by the distribution of the pigment granules), there is no evidence that the pigment produced the death of the cell unless it was excessive in amount The release of pigment by disintegration of heavily charged cells, on the other hand, may indicate that large amounts of it may lead to death of the cell

Pigmentary infiltration, as we have chosen to designate the process, is not infrequently found in association with other types of cellular alteration—sclerosis (pyknosis), acute degenerative changes, edema and ischemic change As will subsequently be emphasized, this multiplicity of changes in a single cell not infrequently occurs, making evaluation of the nature and causes of the end picture a somewhat complicated procedure

Pyknotic Change.—This type of alteration of the nerve cell, which has long been known, and under a variety of names, such as "chronic cell disease" (Nissl), "shrinkage of nerve cells" (Bielschowsky) and sclerotic change, has been found in a number of conditions but is most commonly observed at the margin of areas of softening and recent hemorrhages incident to vascular disease It is therefore only secondarily a traumatic change of the nerve cell, being found most commonly at the margin of traumatic cortical hemorrhages, which constitute a considerable proportion of local contusions Cajal [15] reported this change near the margins of experimental cortical wounds, and Winkelman and Eckel [16]

observed similar cells at the margin of cortical lesions in which vascular change was present

In our cases pyknotic change was almost invariably present, at least to some degree, at the margins of traumatic cortical hemorrhages While a similar change of mild degree was sometimes seen (as has also been observed by Hassin [11]) in cases in which there was extensive cerebral edema, it may be said that in its major and classic form the reaction is essentially a local one It occurs early (within the first few hours after injury) and apparently persists for some time (at least three and one half days in this series) It is possible that such pyknotic cells may be overcome in the advancing marginal zone of degeneration, but undoubtedly individual cells persist for some time, as the shrunken type of iron-encrusted cells of long duration definitely suggests We have found this change to occur typically just distal to the zone of preserved cells, exactly as Cajal observed them in his experimental cerebral wounds

In its typical form the pyknotic cell is shrunken, especially in its long axis, the cytoplasm usually stains a deep reddish or bluish purple, and little structure is to be made out The compressed, elongated and often pyramidal nucleus likewise shows little structural detail, being manifested only by a none too sharply defined clear area in the central part of the cell The margins of the cell, usually fairly regular and smooth, are concave The evident dendrites are few, they stand out sharply, owing to their dark coloration, and the tortuous (corkscrew) apical process can be traced for some distance above the body of the cell These cells are often found in obviously distended pericellular spaces, which betray the presence of excess tissue fluid There is at times an associated shrinkage of the surrounding interstitial tissues

Fusiform Alteration—One occasionally sees small nerve cells which present a fusiform shape in the region next to focal cortical hemorrhages of traumatic origin Because these cells are invariably found in this location, because they are always observed where typical pyknotic cells occur and because they present definite characteristics which suggest this change, it has been assumed that they are but one type of pyknotic cells Since they are small, it is assumed that they are somewhat altered and represent the fusiform (polymorphic) elements which are present in the deep layer of polymorphic cells of the cerebral cortex This conclusion seems to be correct, since these cells are seen in cases with very short survival periods (one hour) Be this as it may, it is sufficient to say that these elements are found in the shape of an elongated oval, presenting an apical and a basilar process, occasionally with a lateral expansion The elongated nucleus is frequently characterized by the presence of a variably sized nucleolus The processes of these cells, especially the apical one, are tortuous With the Cajal reduced silver method, the neurofibrillar substance is usually seen to be varicose or broken up into coarse or fine granulations, or to form a reticular network in the basilar portion of the cell (fig 6)

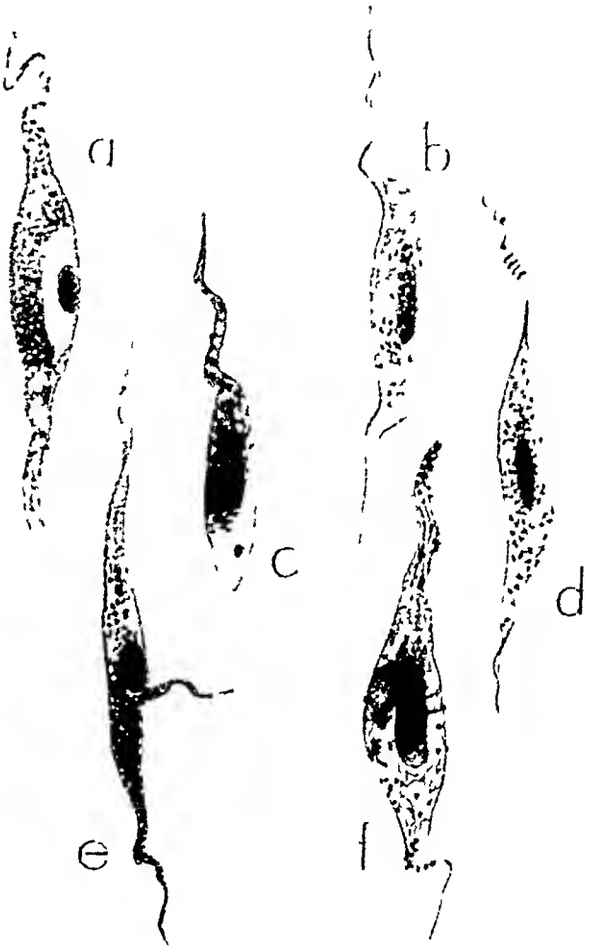

Fig 6—Pyknotic change ("sclerosis") in the bipolar cells in the deeper layers of the cortex adjacent to contusion Granulation of neurofibrillar elements as shown with Cajal's reduced silver method Survival period, about two hours

Because of the location of these pyknotic or sclerotic cells, near the margin of contusion hemorrhages of the cortex, it is not surprising that this type of change is modified with the presence of change of other kinds Not infrequently one finds pigmentary infiltration in cells otherwise typically sclerotic The process of preservation apparently also overtakes cells which have already begun to show this type of alteration (seen in cases with a survival period as short as seven hours and as long as seven and a half days) The occurrence of vacuolar spaces in the basilar portion of some of the cells suggests that pyknotic changes may be succeeded in certain

circumstances by some degree of severe cell change (traumatic degeneration) Some cells which show typical morphologic alterations but in which the cytoplasm stains a pinkish or copper color suggest the further possibility that ischemic change might alter its appearance Some of the various possibilities are indicated in figure 1

As has already been pointed out, this type of nerve cell change is not typical of injury but is one which is found in many circumstances and under many conditions Since it is most common at the margin of areas of softening or local cortical hemorrhages, it is assumed that its occurrence is best explained by some local disturbance in circulation This seems to be demonstrated by the fact that in this series of cases it was typically found at the margins of traumatic cortical hemorrhages and in regions next to focal lesions where edematous change was pronounced Pyknotic change therefore, is only indirectly a post-traumatic alteration in nerve cells, being secondary to such vascular disturbances in the cortex as may by chance be produced by the traumatic lesion, which usually occurs in the form of local hemorrhages

Ischemic Change.—This alteration is rare with traumatic lesions of the cortex and, when present, is invariably due to some associated vascular lesion Neuburger [16] described it as a distant change (hippocampus) following gunshot wounds of the head and attributed it to some general effect of the wound on the intracranial vascular system Winkelman and Eckel [46] described it as occurring near traumatic foci in the cerebral cortex

Ischemic changes as a consequence of traumatic cortical lesions seem to occur in two forms (1) as an atypical, copper-colored cell, found at the margins of very recent lesions, and (2) as a typical ischemic cell, which is commonly observed in the cortex adjacent to a contusion after an interval of seven days or more The cell showing atypical ischemic change is characterized by loss of chromatic substance from the cytoplasm, some degree of shrinkage of the cell and the assumption of a peculiar and characteristic copper color The steps leading to the formation of such a cell, beginning at a short distance from a contusion and extending up to its margin, are shown in color in figure 1 (a^1 to a^5)

The typical ischemic change has been found, in our experience, only after a week or more has elapsed since the time of the injury In a study of a series of sections from the margins of contusions of persons who had survived their injury for an interval of seven to ten days, the cytoplasm of the regional cortical nerve cells was found to present a typical ground-glass, agranular appearance The cytoplasm stained a brilliant orange-pink with eosin The cell body was slightly shrunken and seemed to merge, without much distinction, into the surrounding interstitial tissue, suggesting that a slow process of cell disintegration had already begun The appearance of these cells is indicated in figure 1 (*d*) This change, which may be preliminary to multinucleation, to be described later, is evidently the result of circulatory disturbances at the margin of cortical bruises and lacerations On this basis, it may also be assumed that similar alterations would be found at the borders of cortical softening incident to traumatic thrombosis of the cerebral arteries

It is therefore to be concluded that typical ischemic change is rarely found as an alteration in the cortical nerve cells in case of trauma and then only in response to some traumatic vascular lesion and after an interval of one to two weeks An atypical form of this change, based on the peculiar staining reaction of the cytoplasm of the affected nerve cells, may be seen in which the cytoplasmic change occurs in cells showing other types of degenerative change

Lipoidal Change in Nerve Cells.—Pigmentary atrophy, as the localized collection of pigment in the paranuclear zone of the nerve cells of older persons has come to be called, like pyknotic and ischemic change, must be considered at best only an indirect effect of trauma In any circumstances, its production as a result of trauma is unusual Muhlmann [47] found such changes in the nerve cells of the nucleus of the vagus nerve after injury and assumed them to be of traumatic origin Bianchi [41] found lipoidal change in the nerve cells adjacent to experimental focal injury

While we found evidence of lipoidal change in a number of the cases studied, it seemed clear

47 Muhlmann, M Weitere Untersuchungen uber die Veranderungen der Nervenzellen in verschiedenem Alter, Arch f mikr Anat **58** 231, 1901, Verhandl d deutsch path Gesellsch (1900), 1901, pp 148, Anat Anz **19** 377, 1901

that in most instances it was due simply to the advanced age of the patient and was not to be attributed to injury to the head At the margins of the cortical contusions in some of the older lesions (two weeks or more) some of the nerve cells were found to contain a deposit of lipoidal pigment which stained a bright red with sudan IV (fig 1) This seemed to be an unusual change and was probably a true traumatic effect, since it was found in persons in the third decade of life This conclusion seems to be verified by the fact that it was a local and not a universal, alteration

It is generally agreed that pigmentary atrophy is to be considered a slowly regressive change, indicative of progressive senility This change is probably the result of minor impairment of nutrition, or perhaps, more accurately, of cellular respiration This is suggested by the fact that similar changes have been observed as a relatively acute process in cases of asphyxia in which the patient survived the episode for a few weeks (Courville [18]) On this basis, it may be assumed that any cortical lesion in which there is impairment of tissue respiration may be the seat of lipoidal change in the regional nerve cells Such seems to be the case in some of these focal traumatic cortical lesions which are old enough to permit such changes to occur and about which the necessary disturbance in circulation has occurred On this basis, then, pigmentary atrophy is to be considered a local circulatory change occurring as an alteration incidental to, and not as a direct consequence of, injury

Local Edematous Change in Nerve Cells—Attention has already been drawn to certain minor changes in nerve cells which apparently occur as a generalized alteration as a consequence of traumatic edema of the brain These changes consist in vacuolation of the nucleus and nucleolus, with semilunar perinuclear "halos," which are apparently small circumscribed collections of fluid Rarely, vacuoles of small size may be found in the cytoplasm itself The reason that these changes are so inconspicuous is that rarely does traumatic cerebral edema become so profound as even to simulate the typical picture of edematous cell change observed in animals which have been experimentally hydrated by the intravenous injection of hypotonic solutions

On the other hand, it is quite generally recognized that local edema about regional cerebral wounds is much more pronounced than general edema It is therefore not unreasonable to expect that the local effects of edema on nerve cells will be much more permanent than the general effects One reason that such changes are not better defined is that they are overshadowed by other, and more serious, alterations in the cellular elements Nevertheless, in the vicinity of these wounds, routine stains often disclose more or less conspicuous vacuolation of the nerve cells

Scaglosi [8] found vacuoles in nerve cells twenty-four hours after experimental injuries to the brain The Nissl method was used to demonstrate these vacuoles These vacuolar changes were also observed by Bianchi [11] in nerve cells in the vicinity of experimental cortical wounds Cajal [15] also saw vacuolated neurons in association with experimental injuries of the cortex When the change is extensive, the large, smooth-contoured, round or oval vacuoles come to obscure to a considerable degree the normal structure of the cell [49]

Segmentation of the Nerve Cell—In his now memorable study on the nerve cells, Ewing [32] described clefts and fissures of nerve cells as a type of cell change Similar changes have been observed by us In these cells, which are extensively vacuolated (fig 7), indentations or fissures extend from the margin of the cell into the cytoplasm or nucleus for variable distances In some instances, the fissure passes entirely through the cell, one or more such fissures at times breaking it up into several segments Whether this segmentation is the result of a collection of extracellular fluid which pushes its way into the cell or whether the interruption of cell membrane is a result of rupture of a fluid-filled vacuole is, of course, conjectural At first these observations were thought to be artefacts, due to improper fixation or staining, but on closer study it seems fairly clear that this process of segmentation is simply

48 Courville, C B Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15** 129 (May) 1936, Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif, Pacific Press, 1939

49 It is advisable to point out that the simple presence of vacuolar spaces in the cytoplasm of the nerve cell does not necessarily warrant the diagnosis of vacuolar change As will be shown in a subsequent section, serious degrees of traumatic degeneration of the nerve cell are accompanied with the formations of vacuoles, which often completely fill the cytoplasm of the cell Even when these vacuoles are of fluid nature (which they sometimes are not, being due to inclusion forms not stained by the method being used), one is not privileged to say that their presence is due to edema

an advanced stage of local edematous change which leads to destruction of the nerve cell As evidence for this conclusion are the numerous vacuoles which are already found to be present in the cytoplasm and nucleus,

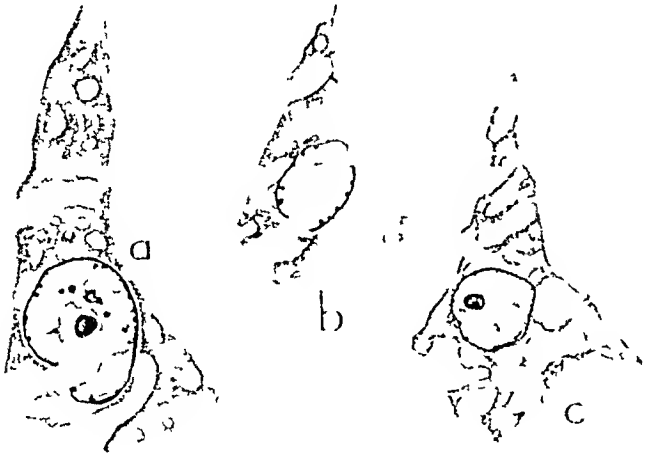

Fig 7—Vacuolation and segmentation of nerve cells adjacent to local cortical injury, apparently the result of local edema Bielschowsky-Plein stain for tigroid substance, Survival period six and three-fourth hours

the apparent rupture of many of these vacuoles through the cell, and even the nuclear membrane, and the ragged appearance of the borders of the cell

Edematous change, therefore, may be a generalized and relatively mild type of alteration of the nerve cell, or it may be extreme, and may even lead to cell destruction when it occurs in the vicinity of a local traumatic lesion of the cortex This change may also be present to variable degrees in cells in which other types of alteration are in evidence

Acute Traumatic Change—By this time it has become apparent that the alterations which occur in nerve cells in response to injury are not in any case greatly different from, and in many instances quite the same as, those which may occur from any other type of pathologic process Perhaps the most disturbing feature in efforts to evaluate the nature of cell change is the occurrence of multiple processes acting on a single cell This principle still holds good for the most typical of the cellular responses to trauma, which may be included under the general heading of "acute traumatic change" Of this type, there may be distinguished three morphologic subtypes, each of which seems to conform to a fairly characteristic pattern But even in these subtypes one is able to trace definite similarities to the various specific types of cell change which are already well known Each of these variants will be briefly described before a more detailed description of the alterations in the various structures of the nerve cell is given

Acute Traumatic Chromatolysis This type of change in ganglion cells is observed near the margins of minor and experimental injuries (Penfield [44]) or traumatic lesions or at a greater distance from the borders of major ones It differs perhaps only in rapidity of development and in degree from those alterations which we have already observed as a general effect of the shock of cranial injury As Hassin [11] has pointed out, it is practically identical with the change which Nissl described half a century ago as "acute disease of nerve cells" This alteration is characterized in cases of traumatic lesions by a minor degree of swelling of the cell, progressive loss of tigroid granules, which begins in the perinuclear region, and eccentration of the nucleus and nucleolus, with alteration in shape of the nucleus due to shrinkage, which results in the formation of folds in the nuclear membrane The cell may subsequently show evidences of the more severe types of alteration if changes to be located in the path of a progressive advance of the zone of degeneration and, as has been pointed out, may show the presence of other types of alteration incident to the traumatic lesion

Acute Total Disintegration At the margins of acute traumatic lesions of the brain are invariably found a number of cells which are evidenced in the preparations of the various methods only by a shadowy outline These cells, for this reason, have been designated as "ghost cells" These cells were noted by Cajal [15] at the margin of his experimental wounds of the cortex They may be found in cases of injury of the human cortex as early as an hour or two of the injury and as late as thirty-nine days after cranial trauma This late occurrence of such cells suggests either that they are capable of surviving longer than their pallid appearance would suggest or that perhaps the change occurs progressively in the margin of these wounds It may also be that the failure of these cells to take stains or to become impregnated with metals may not be a true indicator of their viability, for such cells containing hematogenous pigment have been found at the margins of traumatic cortical hemorrhages Whatever may be their state of viability, these cells constitute a type of reaction to injury, in which the cell seems to fade out of the picture *en masse* This may be due to the fact that the injury occurred at a moment when these individual cells were at a low point in their metabolic or physiologic activity, and the force of the trauma rendered them *hors de combat*, a shock which their more resistant neighbors were able to withstand, at least for the time being

Acute Progressive Necrosis This type of change in the nerve cells, which is found at the margin of traumatic cortical lesions, corresponds fairly closely to the "profound nerve cell change" (*schwere Zellveranderung*) of Nissl, though it is modified somewhat by associated pathologic conditions also acting on it and the speed with which complete disintegration takes place This change is characterized by early evidence of cell death in the form of irregularity of the cell margin, vacuolation of its cytoplasm and rupture of the nuclear membrane,

followed by fragmentation of the processes and disintegration of the cell body This process is evidently one of decadence affecting a cell which was killed by the shock of the injury and/or the traumatizing action of foreign bodies or hemorrhage on the cortex It is therefore found at the margin of the area of destruction and within the zone of progressive degeneration which borders this area Such a degenerative change is usually completed in twelve to fourteen days, at the end of which little evidence is to be found of the structures which originally occupied this bordering zone The change, however, may progressively involve adjacent regions if further disintegration occurs as a result of acute or chronic vascular disorders which are initiated by the traumatic process This is particularly true of cortical lacerations with very irregular margins, in response to which a meningocerebral cicatrix is formed

After this consideration of those special entities which had not already been included with the types of traumatic alteration of nerve cells, attention may now be given to the more detailed changes in the various cellular structures which are the apparent direct result of injury to the regional cortex

Alterations in the Cell Membrane—These changes are found almost exclusively in the cells which undergo acute necrotic changes With the majority of the other types of alteration, the membrane seems to preserve its integrity fairly well In the "ghost cells" the cell membrane, as well as the other characteristic structures of the cell, is not amenable to demonstration with the usual methods of staining and impregnation Satellite cells may pass through the cell membrane in the occasional examples of pseudoneuronophagia which may be found at a little distance from the margin of the wound The membrane may also be interrupted by ingress or egress of large fluid vacuoles, found in cells undergoing "segmentation" as already described Otherwise the change in the cell membrane is largely a matter of disruption of this structure as a natural consequence of progressive disintegration of dead elements at the margin of the lesion This is found as an almost immediate consequence of trauma (within a few hours), associated with the breaking off and fragmentation of the cell processes and, later, complete disintegration of the cell (fig 8) It is possible for only a part of the cell to show these changes at first, suggesting a focal injury of such an element It is likely that such a focal injury is incompatible with the life of the cell and that ultimate destruction results

Changes in the Cellular Cytoplasm—These changes are numerous and variable In this connection, we are concerned only with alterations in the fundamental protoplasm of the cell, not with the contained formed structures, such as the tigroid substance, the neurofibrils or the Golgi apparatus These changes may be described as (1) homogenization, (2) pigmentary and lipoidal deposition, (3) formation of granules and (4) vacuolation

1 Homogenization in the region of focal injury seems to be a modified form of ischemic cell change, described by Spielmeyer The cytoplasm loses its tigroid material and thus becomes agranular This is followed by a uniform ground-glass appearance of the cytoplasm, which assumes first a bright pink and then an orange-pink copper color These progressive changes can be observed in a single case by first studying the elements removed from the influence of the trauma and then noting the changes as one approaches the margin of the contusion This is best seen, according to our experience, in cases with a survival period over twenty-four hours, a fact which suggests that time is a factor in the development of these characteristic changes Cells of this type immediately adjacent to the margin of the lesion often show vacuolation at the base of the cell, suggesting that degenerative changes of a more acute variety had supervened

2 Pigmentary deposits were of two types Pigmentary infiltration, with the collection in the cytoplasm of hematogenous pigments in the margin of traumatic cortical hemorrhages, was the rule in cases of such an injury, a process which has already been described in some detail Such pigment may apparently undergo regressive chemical changes within the cell, for after a week or more bright yellow granules may be found in cells at the margins of recent hemorrhages Pigment atrophy (lipoidal change), characteristic of advancing years, may be found in the ganglion cells of older persons, in which it is an incidental change, and not a consequence of injury However, a similar development may occur in younger persons at the margins of cortical contusions and lacerations at the end of two weeks It is suggested that this is due to vascular change which results in a degree of cellular anoxia, since similar changes do occur as an effect of asphyxia (fig 1)

3 The occurrence of abnormal granular products is almost exclusively an evidence of acute degeneration of nerve cells and is found in such elements after several days in phosphotungstic acid hematoxylin and aniline blue preparations These granulations are found to be fuchsinophilic or basophilic in reaction and are usually round or slightly oval and small They are found in the cytoplasm of the nerve cells which show other evidence of cellular disintegration

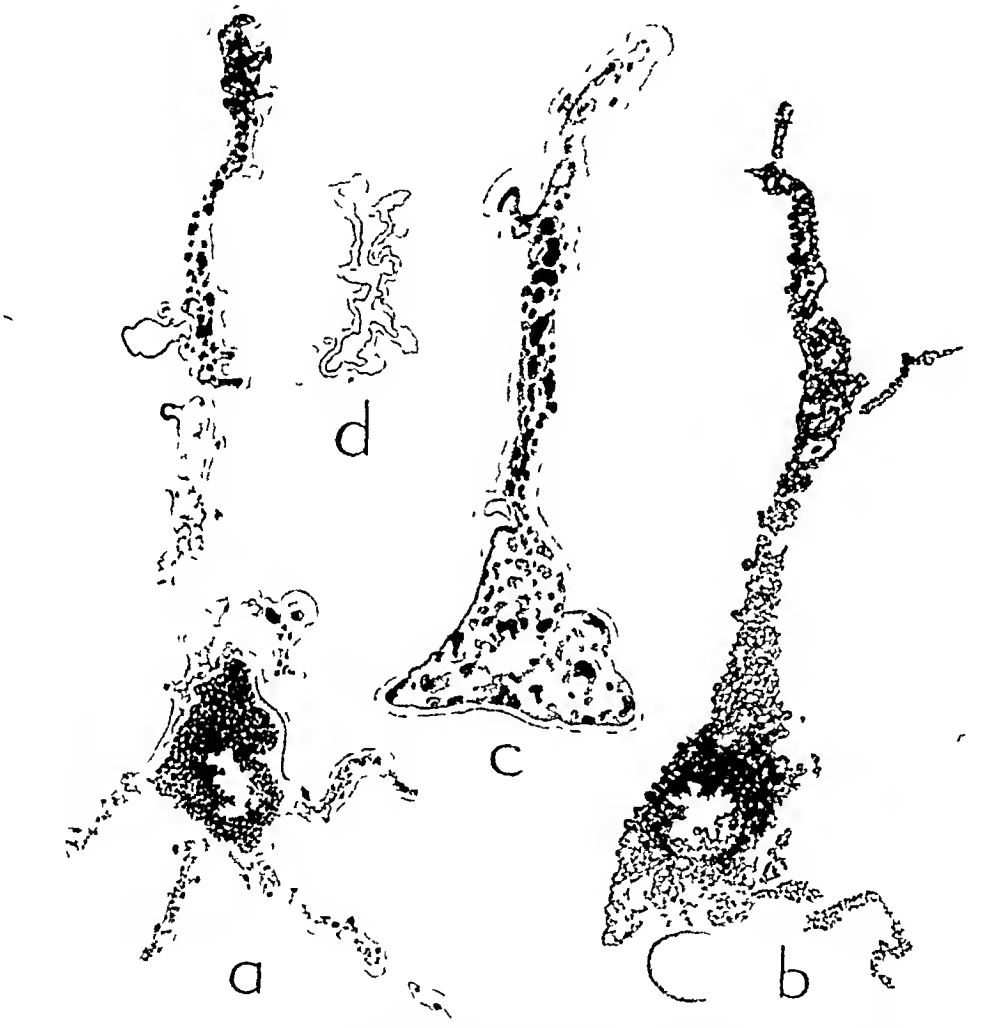

Fig 8—Disintegration of nerve cells ("traumatic degeneration") in the vicinity of a cortical contusion, showing fine (*a* and *b*) and coarse (*c*) granulation of the neurofibrillar elements Cajal's reduced silver preparation, survival period, thirty-five days

4 The formation of vacuoles in the cytoplasm of the nerve cells at the margin of an injury has a varied significance In cells undergoing acute necrosis, such vacuoles may represent spaces or defects in the cell, for no staining method brings out any positive physical structure These spaces are small at first but increase in size progressively as the cytoplasm breaks down Special stains will show, at the same time, the presence in the cytoplasm of fuchsinophilic and basophilic granules of smaller size, and usually in the basilar portion of the cell Such granulations are also represented by the formation of vacuolar spaces in the cytoplasm in routine preparations Vacuolation of the nucleus, the nucleolus and, at times, the cytoplasm of the cell is found most often as a consequence of edema In the presence of severe wounds, this process may be present to a degree in which vacuolation of the cytoplasm also occurs This begins at first with the formation of semilunar clear spaces about a portion of the nucleus Then vacuoles are formed in the cytoplasm in the basilar portion of the cell With extremely severe wounds vacuoles of this type completely fill the cell, contributing in some instances to "segmentation" of the cell, as described elsewhere

Changes in the Tigroid Substance—Changes in this substance occur as one of two types (1) dissolution, or chromatolysis, and (2) fusion, or agglutination, of this material Chromatolysis is evidently the simplest type of reac-

tion of this substance and occurs in the nerve cells at the margins of simple puncture wounds or minor contusions This process usually begins in the perinuclear region, where a clear zone is formed As the process spreads concentrically, the larger granules are broken down into their finer constituents, leaving a ring of fine, dustlike particles Tigroid material then disappears from the basilar region of the cell and finally from the apical region, where it tends to persist the longest Ultimately, even the fine bluish granulation disappears, leaving an agranular cytoplasm

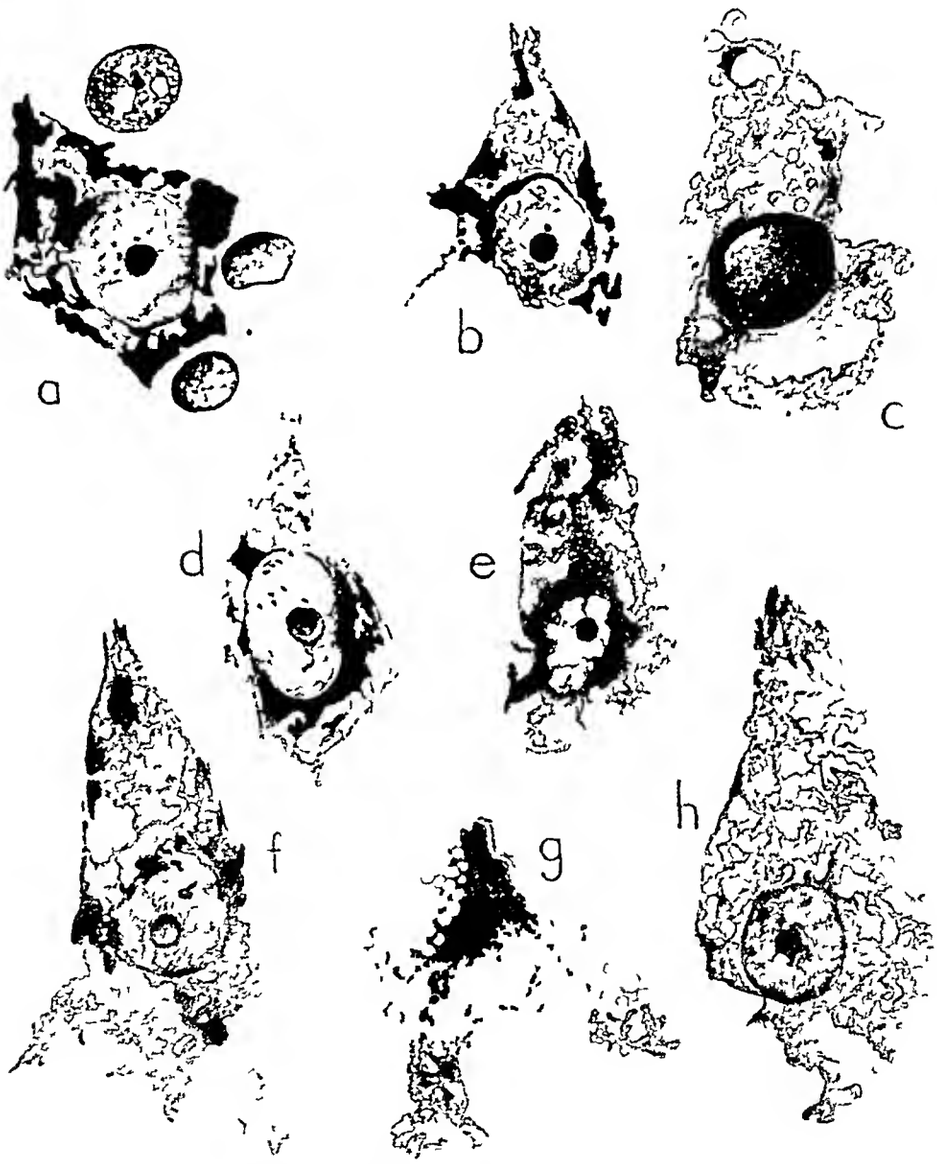

Fig 9—Condensation of chromatin material (tigroid substance) in nerve cells in the vicinity of a cortical contusion, showing associated vacuolation and fenestration of cells, (*f*) deposition of lipid pigment Bielschowsky-Plein method for Nissl substance, survival period, three days and nineteen hours

Fusion of the tigroid granules seems to be a process associated with acute traumatic degeneration of nerve cells, being found after two or three days in those elements destined to disintegrate This is evidenced by the marked irregularity of the cell outline, the occurrence of vacuolation of the cytoplasm and the breaking up and disappearance of the nucleus In these cells the chromatic granules tend to lose their characteristic shape, size and structure, assuming the appearance of irregular masses of a deep blue appearance and a homogeneous, waxlike structure (fig 1) At times, these large, irregular masses occupy a goodly portion of the remaining cytoplasm, at others, only one or two isolated masses are left Occasionally, the perinuclear granules fuse to form a dark, irregular ring about what remains of the nucleus It is assumed that the necrotic process has resulted in some chemical change in the tigroid substance, causing it to "melt" and fuse into these irregular masses These changes are shown in figure 9

Alterations in the Neurofibrillar Structure — These changes are interesting and complex It must be recognized that the changes observed

in the reduced silver preparations differ much from those in sections prepared with the Bielschowsky method In order to compare Cajal's observations in experimental wounds, it seems best to describe them human counterpart on the basis of this staining differential

Cajal described several types of alterations in the neurofibrils of his experimental animals The first changes seemed to be hypertrophy and varicosity of individual elements, followed by breaking up of these segments into fusiform fragments This process was followed by the formation of coarse, and then of fine, granules Rarely, a reticular formation seemed to result from the central neurofibrils At times, this disintegration first involved the periphery of the cell, leaving an external clear zone (hirudiform change), in other instances, the central portion of the cell was first affected It is reasonable to believe that this is the typical process in the disintegration of these elements Since injury was due to simple incision of the cortex, blunt force did not enter into the problem

A somewhat different situation exists in the case of injuries to the human brain With contusions and lacerations of the brain, the element of shocking force is introduced, which was not present in the simple cortical incisions of Cajal It has therefore been found that there is an almost immediate granulation of the neurofibrils in the cells at the margins of acute cerebral wounds In other words, the injury to these cells is so profound as to produce the end stage of disintegration at once However, in the cells more distant from the margin of the traumatic lesion, one is able to find varicosity and fusiform degeneration after a few days, followed, in turn, by coarse and fine granulations Since reticular formation has also been observed, we have been able to find in the injured human nerve cells all the counterparts of the changes described by Cajal

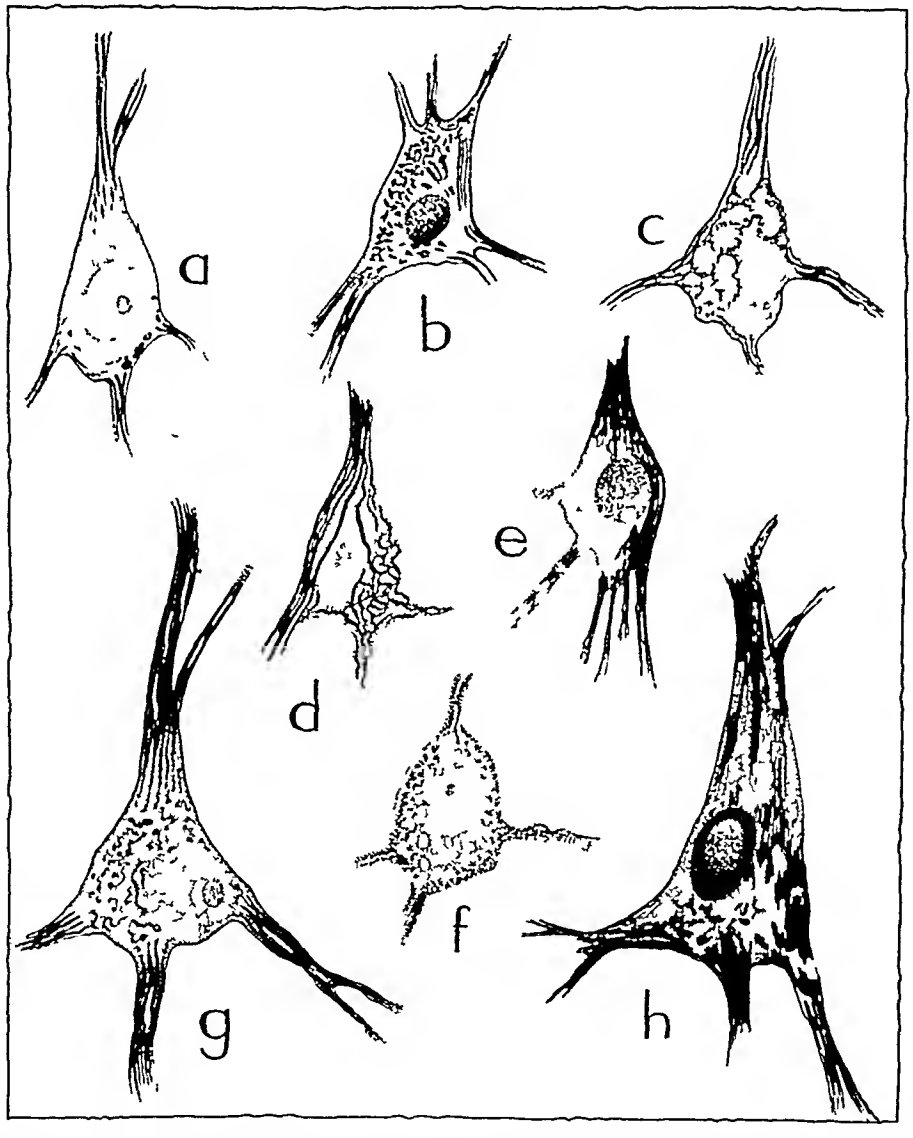

Fig 10—Alterations in the neurofibrillar pattern in nerve cells as a result of trauma, showing (*a*) fine granulation, (*b*) coarse granulation, (*c*) tortuosity and net formation, (*d*) varicosity and reticulation, (*e* and *h*) patchy degeneration, (*f*) fine and coarse granulation and (*g*) fragmentation Cajal's reduced silver stain, survival period, thirty-one hours

The appearance of individual cells differed greatly As is shown in figure 10, the central portion of a cell may be completely devoid of any normal fibrils, or even of the larger residual fragments of them In other cells small fragments, either lying loose in the cytoplasm or gathered about vacuolar spaces, could be seen In these cells fairly well preserved elements were to be seen in the processes In some cells both fine and coarse granulations, resulting from disintegration of these elements, were observed Some cells presented a peculiar patchy, or barred, appearance, which was due to spotty coarse granulation Individual intact fibers may be hypertrophied and varicose to a conspicuous degree Occasionally, bizarre patterns may be formed by the fragments of these elements Some of these alterations in individual elements are shown in figure 11

All these alterations, whether they are gross or detailed, seem to be more advanced in the smaller pyramidal cells than in the medium-sized or the large ones These smaller cells are evidently more susceptible to the effects of injury

In the Bielschowsky preparations, a rather less intense, and somewhat delayed, disintegra-

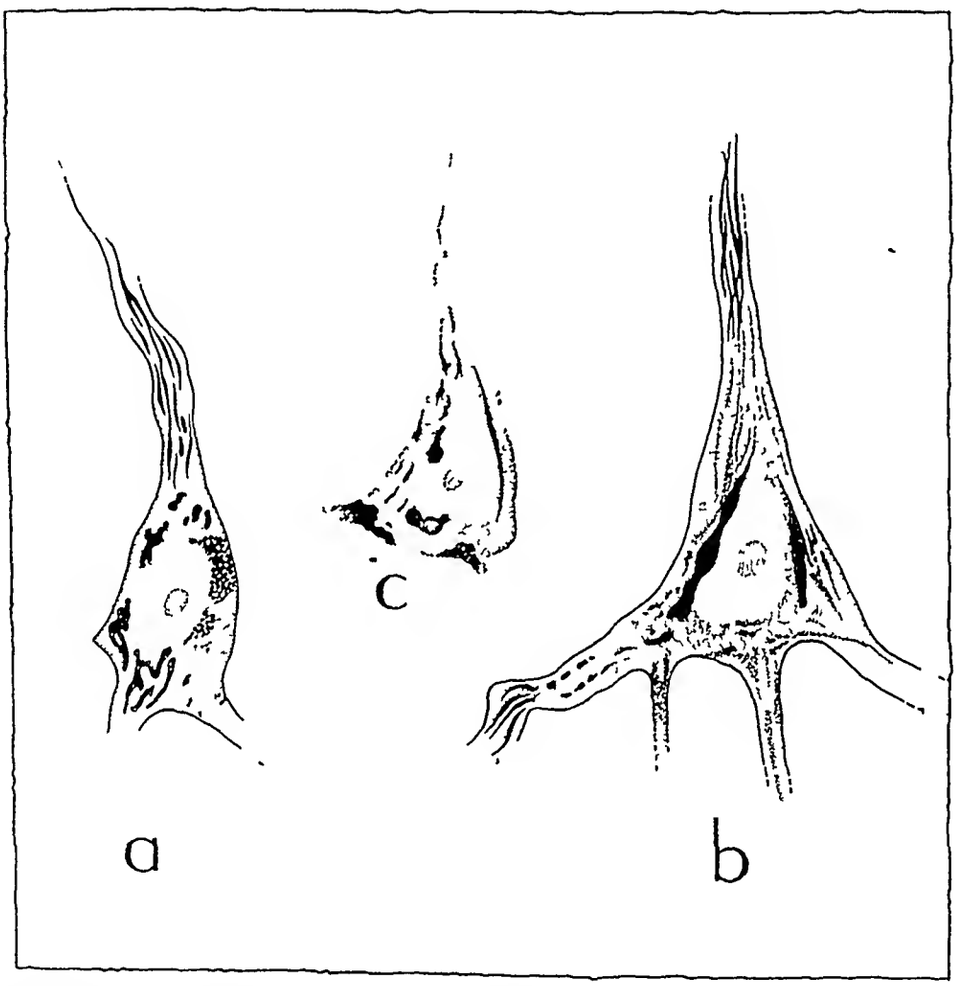

Fig 11—Alterations in the neurofibrillar patterns, showing details of fragmentation and granulation (*a* and *c*) and swelling and varicosity (*b*) Cajal's reduced silver stain

degeneration of entire groups of fibrils, for which no specific reason can now be assigned

A study of individual fibrils brings to light some interesting observations as to the process of disintegration of these structures Although as a rule all of the fibers in the body of the cell are affected alike, this is not invariably the case One may see fairly normal fibers passing through the cell body occupied largely by the granular remains of these elements Or one may observe a number of fusiform granules along with fine or tion of these elements is present The neurofibrillar elements do not show early alterations and seem to pass through a different series of steps in the process In some cells the formation of a peculiar reticular network seems to be an interim stage In other cells what seems to be the formation of tiny vacuoles within or between individual fibers (observed under the oil immersion lens) seems to take place before degeneration occurs Hypertrophy and varicosity are much less evident, although they, too,

may be present in preliminary stages to complete disintegration with both methods

Nuclear Changes—These occur as alterations in the size and shape of the nucleus, the development of vacuoles in its substance and the appearance of certain peculiar alterations in the chromatin elements The nuclei of regional nerve cells may undergo shrinkage (evidenced by the occurrence of folds in the nuclear membrane), associated with alterations in their shape, as has been pointed out in the general traumatic changes of nerve cells The nuclei, as well as their nucleoli, may also become eccentric in the simple chromatolytic form of change In the presence of edema, vacuoles may develop in the chromatin material, forming odd maplike patterns Even the nucleoli may contain one or more tiny vacuoles, visible only under the higher powers of the microscope Peculiar chromatin condensations (already described in the section on general changes) may also be found, apparently a general response to injury, even though it may be present within the shadow of a local wound Degenerative alterations in the form of variability in thickness of the nuclear membrane, rupture of the membrane, with loss of its contents, and ultimate disintegration of its contained structures are to be found with acute traumatic degeneration of the cell

Multinucleation of Nerve Cells—The occurrence of what seems to be abortive efforts at cell division on the part of neurons as a response to cortical wounds has been known for many years The concept of mitotic, as well as direct, nuclear division in nerve cells was introduced by Mondino,[50] who saw karyokinetic figures in these cells about the margins of stab wounds made with a hot needle in the brains of young guinea pigs These experiments were repeated by Coen,[51] Sanarelli[52] and Tschistowitsch,[53] all of whom found mitotic figures in the nerve cells in the vicinity of the cortical wound In his observations Friedmann,[54] who studied the reactions to various traumatizing agents in birds, as well as guinea pigs and puppies, noted that karyokinesis was present essentially in its first stages and that this process did not lead to the formation of double cells This observation was also made by Levi,[55] who stated that mitosis in nerve cells proceeded only through the first phase That mitosis did occur in nerve cells seems to be clear, as indicated by the drawings of Tschistowitsch, who likewise stated that this phenomenon did not lead to the formation of new nerve cells It is therefore difficult to account for the conclusions of Vitzou,[56] who asserted that he found new-formed nerve cells and fibers at the margin of resected occipital lobes of pigeons and young apes Borst[57] found mitoses in nerve cells in the vicinity of foreign bodies (pyroxylin) inserted into the cortex of dogs Utilizing the factor of irritation, in addition to that of trauma, Schreiber and Wengler[58] and Ranke[59] injected scarlet oil into the brains of experimental animals and were thus able to verify the observations of earlier investigators Schreiber and Wengler, in particular, were able to trace mitosis through the various intermediate phases to complete cell division

However, long before all this experimental work on trauma to the brain had been carried out, what was considered to be multinucleation of nerve cells in the vicinity of wounds in the human brain had been observed by Jolly,[37] Tigges,[36] Ceccherelli[38] and Popoff[39] These observations, being described as incidental, had apparently been lost sight of entirely, however, when we first found nerve cells with two or three nuclei at the margin of recent contusions of the brain, in the course of our initial studies, in

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1932[60] We were quite unaware that any one else had seen them before The previously reported observations of mitoses in nerve cells in experimental wounds and multinucleation in the margin of old wounds in the human brain were subsequently brought to light by a study of the original contributions on the subject of experimental injury to the brain in general and of the work dealing with evidences of regeneration after injury of the parenchymatous elements of the brain When Gaupp[61] reported multinucleation of nerve cells at the margin of rather old traumatic lesions of the brain (all sixteen to seventeen years old), he was evidently unaware of this observation by previous students of cerebral injury Gaupp concluded that this manifestation was a local response to injury of the brain and probably represented an abortive attempt at cell division, although the phenomenon might also be related to a regressive change

In 1 of our cases many of the nerve cells just a step removed from the fairly sharp margin of a recent contusion of the prefrontal cortex showed evidence of direct nuclear division after a survival period of fourteen days In some cells this was manifested by an indentation or constriction of the nuclear membrane, a process which was apparently preceded by duplication of the nucleolus In others the parent nucleus had been completely divided into two daughter nuclei, often with some spatial separation of the two elements (fig 12) In some individual cells one of the two nuclei showed further evidence of budding, at times a third form was seen No detectable morphologic change could be seen in the enclosed chromatin material to suggest any specific relationship between this substance and the process of nuclear division

In a second case, in which the patient survived his injury fifteen days, the process seemed to be somewhat further advanced In many cells three distinct nuclei were found, all of about the same size and structure This asymmetric, or eccentric, nuclear division indicated that the regenerative faculty, whatever is the structure in which it is resident, was not equally spread throughout the original nucleus but was usually transmitted in greater part to one of the two daughter nuclei These cells seemed to be situated somewhat closer to the margin of the contusion than the cells in the first case, but this is perhaps without significance The individual cells also showed more evidence of regressive change, both as to the cytoplasm of the cell and the nucleus After three weeks, four nuclei were only occasionally observed

Multinucleation of nerve cells was observed also in cases with survival of twenty-one days (contusion), thirty-eight days (laceration) and seven months (intracerebral hemorrhage) This would indicate either that the process, once begun, was continued over a long period or that the cells so altered remained in this state for a long interval The occurrence of a considerable degenerative change in the cells so affected seemed to indicate that these cells were destined soon to undergo complete dissolution, by analogy, one might presume that the remaining

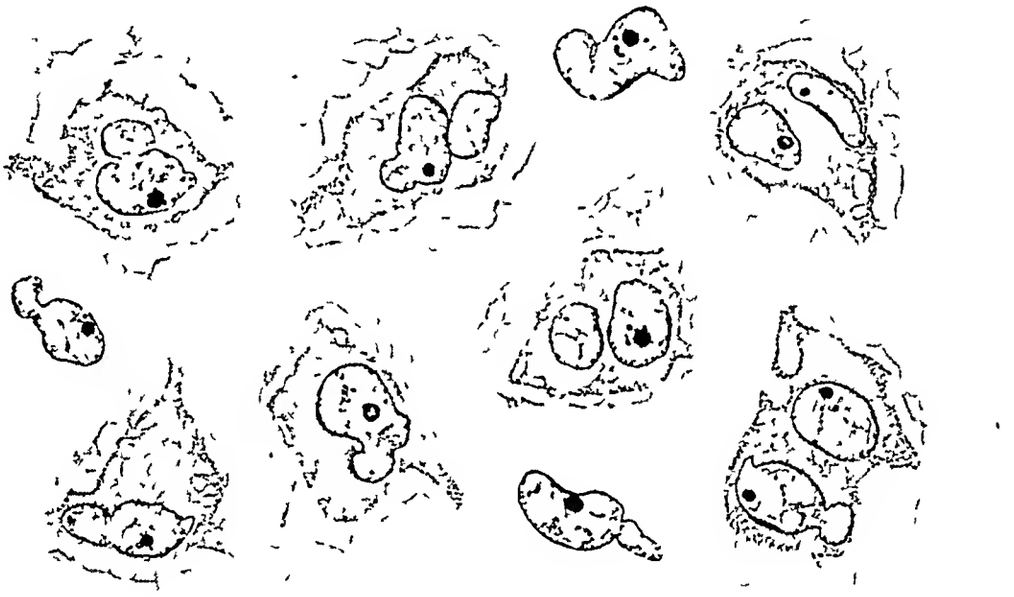

Fig 12—Multinucleation of nerve cells at the margin of a contusion Hematoxylin and eosin stain, survival period, fourteen days

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cells in the vicinity of these traumatic lesions sooner or later might be affected by the process, which seems simply to be a prelude to their effacement As Gaupp [61] has pointed out, this process may be observed as late as seventeen years after the injury

As a study of the occurrence of multinucleation in older traumatic lesions of the brain, we undertook the investigation of the reaction of nerve cells in the vicinity of old contusions of the brain in 10 consecutive cases which have come to our attention in the Cajal laboratory Nerve cells with two, sometimes three, nuclei were found at the margin of the lesions in every case This observation would suggest that the response is not a rare and incidental change but one of the characteristic reactions to injuries of the cerebral cortex It was not present in a case of an old contusion of the cerebellar cortex, suggesting that the Purkinje elements do not have a similar propensity in this direction

These evidences of regressive change were both acute and necrobiotic, as well as subacute, and even chronic In addition to the irregularity of the cell margin and the rupture of the cell membranes of the nucleus, which suggested prospective dissolution of the cell, there were in evidence vacuolation of the cytoplasm and nucleus, suggestive of advanced edematous change, and abundant lipoidal pigment in the cytoplasm (indicative of a local, and possibly vascular, change, in view of the relative youth and short survival period of both patients) These changes were associated ones, due to the injury or to its immediate consequences, and were not specifically related to the process of nuclear division

When these observations are reviewed in the light of the presence of only two-nucleated cells at the margins of older cerebral wounds, the possibility is suggested that this further ability to division of one of the daughter nuclei is limited to the acute phases of the injury, a process which may be stimulated by the presence of decadent material, which is presumed to serve as a chemical stimulus to the regenerating activities of the interstitial cells It is also possible that this process of nuclear division is a continuous one, which may persist for weeks or months after the injury has been sustained The only alternative to this conclusion is to assume that these binucleated cells are capable of survival for considerable intervals, a conclusion which is of doubtful validity because of the presence of advanced degenerative changes obviously present in the affected cells While in some instances what seems to be an initial effort at cellular (as well as nuclear) division is found in the form of local indentation of the cell body, at times with some early alterations in the conformation of the cell, no positive evidence that actual cell division did occur was observed This would conform to the conclusions made by investigators who have observed mitotic figures after experimental trauma to the effect that such abortive efforts did not lead to the complete formation of new nerve cells

In the case of multinucleation of human nerve cells in response to local injury, it must therefore be concluded that these alterations are but the latent manifestations of the potency of the cell, not entirely static, which leads to incomplete (abortive) cell division The process is limited to nuclear division, with possible minor morphologic evidence in the direction of division of cellular cytoplasm as well Obviously, the process does not lead to any physiologic restoration, in fact, the cell in which the process occurs is very likely functionally useless, if not actually dead

Ferrugination ("Calcification") of Nerve Cells —Although "calcification" of nerve cells was one of the first of the types of cellular change to be noted as a consequence of trauma, being reported as such by Virchow [35] in 1857, and subsequently noted anew by Friedlander, it is by no means limited to traumatic lesions Ernest also saw them about cortical wounds Spielmeyer [62] stated that this change is found commonly in areas of softening secondary to arterial occlusion or other circulatory disorders, as well as in old encephalic foci and in the region of abscesses He observed it in cases of dementia paralytica, especially of the juvenile variety, in which the Purkinje cells of the cerebellum may be so altered These cells may also be affected in degenerative atrophies of this organ Freeman [63] has shown a large group of such cells in the margin of an old wound of the brain

For many years the dark coloration of these cells led to the belief that these cells were calcified, but more recently it has come to be recognized that they are actually encrusted with iron Moreover, it has also come to be recognized that the process, while chronic in its duration, may take place in relatively recent lesions For example, Cajal [15] found this process taking place in nerve cells not far removed from the margins of experimental wounds in the brain after four-

62 Spielmeyer, W Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, pp 43, 44 and 456

63 Freeman, W Neuropathology The Anatomical Foundation of Nervous Diseases, Philadelphia, W B Saunders Company, 1933, pp 25 and 26

teen days, although it had apparently reached its climax between the twentieth and the twenty-fifth day

This change in the nerve cell is obviously not primarily traumatic, since it is found in so many other conditions The presence of such alterations so typically at the margins of areas of softening due to vascular obstruction suggests that deprivation of oxygen is probably at the basis of the process This is suggested by the observation of many such cells in areas of cortical softening due to asphyxia, as found in cases after a suitable interval of survival (Courville[48]) The presence of such cells at the margin of old cortical scars is a common observation and is probably to be accounted for by the disruption of the local circulation as an effect of disorganization of the regional nerve tissue by the contusion or laceration[61]

These iron-encrusted cells (they are beautifully demonstrated with the prussian blue method) are usually found in small groups in the cortex at the margin of defects consequent to old contusions Sometimes a considerable number of such cells may be found within a limited area, at other points only one or two scattered elements are to be seen The cells are small and shrunken and stain a deep blue with hematoxylin If a group of them are found together, they are more closely approximated than are normal nerve cells, and it is suggested that this is due to absence of the interstitial tissues, which had disintegrated as a result of lack of oxygen The atypical position of individual cells also indicates that some disorganization has taken place

Even with higher magnifications, there is little detail of the cell to be made out At times the site of the nucleus is evident by a central pale area Otherwise, the cells stain a uniform or mottled pinkish lavender to a deep bluish purple, close inspection shows small nodulations on the cell body and its processes These apparently represent small masses of iron, which may be few, or, at the opposite extreme, may completely cover the cell Because of the definiteness with which these cells are demonstrated, the proximal portions of the major cell processes are also well shown They are frequently broken off ("fractured"), with sharp edges, suggesting that this process has made the cells brittle in texture The small size of the cell, its shrunken appearance and the tortuosity of its apical dendrite suggest, further, that in the process the affected cells may have gone through the sclerotic type of change (fig 13)

These cells are obviously dead and in this mummified condition are capable of survival for many years It is for this reason that they are found so typically in the margin of old scars

Summary—Local changes in nerve cells follow a variety of patterns, which are dependent not only on the original traumatizing force but on a number of circulatory changes which follow in the train of the injury—hemorrhage, edema, ischemia and probably some degree of local anoxemia These changes are therefore reminiscent of the alterations in ganglion cells which follow other pathologic processes, except for the interesting observation that evidences of multiple types of change may be found within a single cell

From a practical standpoint it is realized that cells which are engulfed in the general debris of the area of disintegration are immediately destroyed and all trace of them is gone forever Moreover, the cells within a bordering zone of destruction are immediately killed, although their identity may be maintained for several days by the process of "preservation," the result of action by some antiautolytic substance diffused through the adjacent tissues from the blood plasma of the local clot Other dead cells fade out of the picture usually within a short time ("ghost cells"), still others undergo a slower process of active traumatic disintegration, perhaps the most characteristic of all the traumatic changes Distal to this bordering zone are cells which are affected by various types of change, which are to a great extent reversible In some cases at least with a survival period of two weeks or more, the nerve cells make an abortive attempt at regeneration, as indicated by the direct division of the nucleus into double or triple daughter nuclei The cells themselves apparently do not divide Evidences of this abortive reaction may be found months or years after the injury

It seems likely that some cells may persist but with an abnormal function, an assumption based on the occurrence of epileptiform convulsions which have their origin in groups of cells at the margins of old wounds which discharge abnormally according to the electroencephalogram The physical counterparts of this abnormal physiologic activity could not be determined from the material available for the present study

GENERAL CONSIDERATIONS

In the investigation of this series of alterations in nerve cells which result from the general, as well as the local, effects of injury, certain facts

64 Rand, C W, and Courville, C B Iron Encrustation of Nerve Cells in the Vicinity of Traumatic Lesions of the Cerebral Cortex, Bull Los Angeles Neurol Soc, to be published

have become apparent In an effort to evaluate these changes in the light of clinical observations, some fundamental considerations, as discovered by these studies, will be briefly outlined

1 Death of an injured nerve cell may be immediate or delayed If death of the cell has come as an immediate effect of the injury and the cell lies within the area of destruction, it may undergo immediate disintegration in the damaged nerve tissue, its remains being completely obscured by the attendant hemorrhage If the dead cell happens to be at the margin of this area, it may persist with relatively no morphologic alteration for a week or more, owing to the action of some antiautolytic ferment which is present in the blood plasma ("preservation" necrosis of Cajal) Still other dead cells quite promptly fade out of the picture *en masse,* being found as "ghost forms" within a few hours after the injury, and are thought to disappear within a few days, although an occasional cell of this type is still found after five weeks The last group of dead cells undergo, sooner or later, progressive structural degenerative changes, which may be described as progressive traumatic disintegration

2 Most cells outside the area of primary destruction and the bordering zone of secondary destruction are able to survive the shock of injury, although death may overtake them later These cells may show either local or general effects of injury Local effects may be evident in nuclear change, damage to a certain portion of the cell or loss of some of its processes The entire cell may also be affected, as manifested by loss of tigroid substance shrinkage, certain physicochemical changes in its cytoplasm or infiltration of hematogenous pigment It is believed that these changes are not necessarily fatal but may be recovered from if no other pathologic process adds insult to the injury This physical recovery of an injured cell has been appropriately termed "reversible reaction"

3 It is also possible that some cells may survive in an injured state so that they are no longer of any value to the organism's economy Not only may such cells contribute nothing to the normal functioning of the brain, but they may be the source of abnormal electric discharges responsible for post-traumatic convulsive seizures

4 Through a peculiar provision of nature, dead, as well as crippled, cells may be preserved for months or years by being encrusted with iron (ferrugination, often miscalled "calcification") Such cells are commonly found at the margins of old contusions and lacerations of the brain Their death, however, is probably due to an attendant circulatory disorder (anoxemia), since they have been found with many other lesions, especially with softening due to vascular occlusion and after asphyxia

5 In all these changes, it has been observed that there is an individual susceptibility to injury, as to any other disease process In a group of nerve cells, one cell may be found to undergo immediate dissolution (as a "ghost form") or to show severe effects of damage, while

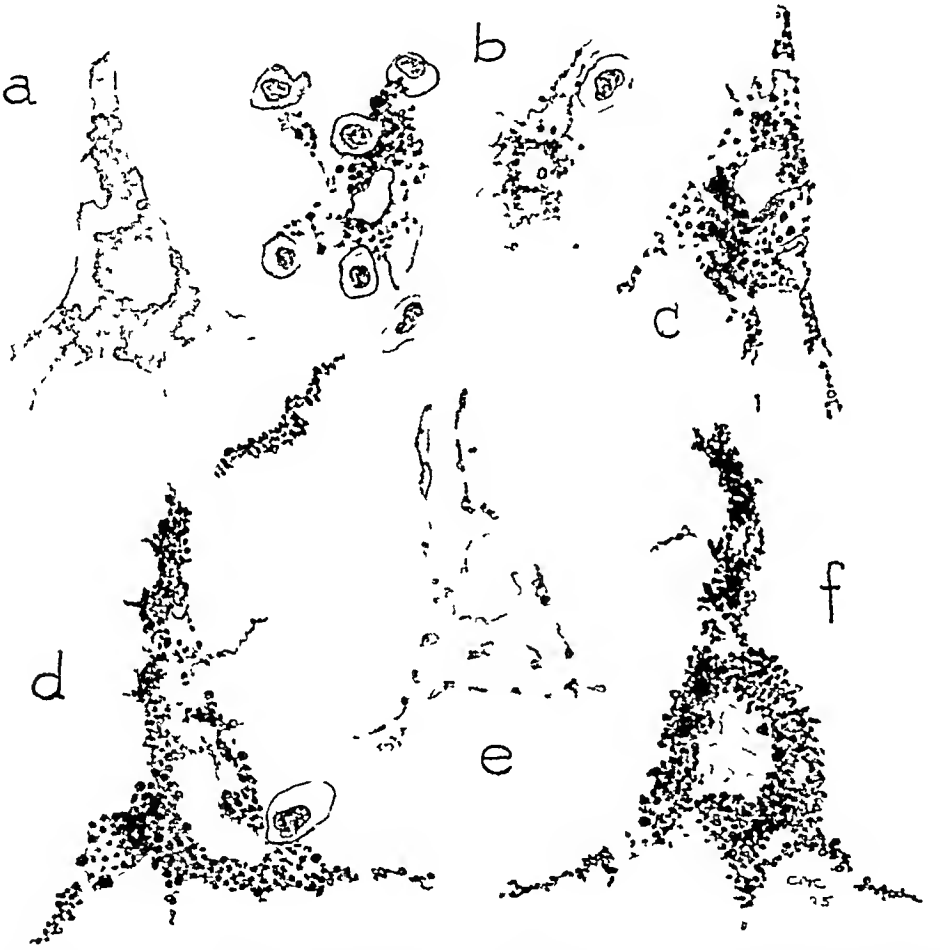

Fig 13—Iron encrustation of nerve cells (ferrugination, "calcification") as found at the margins of old contusions of the cerebral cortex (*a*) Preliminary stage, before iron is deposited, (*b*) early stage, showing presence of phagocytes engulfing broken processes of cells (dendrophagocytosis), (*c, d* and *f*) various degrees of encrustation, (*e*) "ghost form," in which the scarcely visible cell is outlined by granules of iron Hematoxylin and eosin stain

the other cells may be morphologically intact It is assumed that this variable susceptibility to pathologic processes is due to the particular state of the metabolism of the cell at the moment of injury

6 It is likely that the speed with which the destructive process affects the cell has something to do with its appearance at the time it is studied While there are exceptions to this rule (i e, preservation necrosis), other things being equal, regressive changes will be more prominent and sooner terminated adjacent to the local cortical lesion than at a little distance from it, even though the cells in both areas are ultimately destined for destruction

7 A single cell may present evidence that more than one necrobiotic process may be affecting its structure It has been pointed out that as a general effect of craniocerebral injury, nerve cells of the cortex may show both loss of stainability (presumed to be due to the shocking effects of the injury) and the occurrence of cytoplasmic (rare), perinuclear, intranuclear or even nucleolar vacuolation (suggesting the action of cerebral edema) In reaction to local wounds, these combined effects are even more evident Pyknotic (or sclerotic) change, for example, may be found in a cell which also shows the effects of preservation necrosis, pigmentary infiltration, ischemia, edema or even acute traumatic degeneration (cytoplasmic vacuolation with disintegration of the cell membrane) This combination of abnormal changes makes it difficult at times to classify categorically the nature of cellular change

8 The multiplicity of changes possible in nerve cells, or in even a single cell, makes it evident that such alterations are due not only to the original shocking force of the injury but to the attendant hemorrhage, impaired circulation (ischemia with consequent anoxemia) and edema

9 Not only do death and injury of nerve cells occur as an immediate effect of the injury, but, in addition, progressive change may take place in nerve cells as a result of processes which are initiated by the injury and which continue for a variable time thereafter This is true to some extent even in the case of simple wounds (puncture wounds or contusions) but is much more evident with extensive lacerations of the brain, such as follow gunshot wounds The exact cause of these phenomena in simple wounds is not clear, but it is presumed to be minor local changes in the circulation and the formation of the regional scar This seems to be more definitely the case with lacerations, in which contraction of the central scar appears to result in intermittent vascular spasm with local ischemia and cell injury or death As an immediate evidence of this progressive change even in recent injuries, one may find that a cell which has begun to react from the effects of injury is being overtaken by degenerative changes

10 Multinucleation of nerve cells, which is found as early as two weeks after the initial injury is sustained and which may be evident at the margins of cortical lesions many years old, is a process which indicates an inherent recreative ability in elements which are generally considered to be biologically static This process is incomplete and eccentric and does not lead to useful regeneration of nerve cells

11 There is as yet no definite way of determining the degree of normal function resident in a nerve cell on the basis of its physical structure There seems to be some relationship between the severity of the general effects of injury and the amount of Nissl substance still resident in the cell at the time of examination, but whether this change is entirely to be accounted for on the basis of the initial shock of the injury, or whether it is due in part at least to other attendant situations, cannot be stated with certainty Marked changes of the same degree as a result of local injury have been found apparently to be responsible for abnormalities in the electric discharge from the region, as determined electroencephalographically

12 It is as yet unsafe to say that a normal morphologic condition is always an indicator of normal function It is therefore possible that abnormal electric discharges responsible for post-traumatic epilepsy may have their origin in cells which to all appearances are structurally normal Determination of the facts in this situation is outside the realm of neuropathology, as an isolated science, at least with the diagnostic facilities now at hand It may well be that facts of importance in this field can be learned if the pathologist will work in conjunction with the physiologist, making a comparative study of the structural changes in the nerve and the nature of electric discharges, as determined electroencephalographically

These general considerations as to the histologic alterations in cortical nerve cells which occur in consequence of focal traumatic lesions are found to apply in many respects to the other cellular elements as well In this sense, the traumatic changes in nerve cells tend to follow a general pattern They may be immediately destroyed, they may undergo subsequent (delayed) dissolution, they may be seriously damaged and persist in crippled form, or they may sustain only minor injuries, from which they may recover (reversible reaction) The specificity of the changes in nerve cells are based on their different inherently functional character, their great susceptibility to noxious influences and, in particular, their difference in structure The highly specialized function of the ganglion cells, their greater delicacy of structure and their inability to react by reproducing themselves in the presence of necrobiotic processes, account, in the last analysis, for the current, as well as the ultimate, histologic picture that these cells present in the cortex which has been subjected to physical damage

SUMMARY AND CONCLUSIONS

As a result of craniocerebral trauma, certain changes may result in the structure of the cortical nerve cells of the cerebrum and cerebellum These changes may be general, as a result of shock of the original traumatizing force (chromatolysis) or consequent to the generalized edema (vacuolation) which so often follows such injuries in civilian life More noteworthy, because of their variety and degree, are those alterations which are the direct result of focal injuries of the cortex Among the various local cellular reactions may be named preservation necrosis (retention of normal structure by dead cells),

pigmentary infiltration (which is found in the vicinity of traumatic cortical hemorrhages), pyknotic, ischemic or sclerotic change and lipoidal degeneration (all resulting from local circulatory disturbances), a modified edematous change (incident to local edema following contusion or laceration), acute traumatic change (which may occur in the form of acute traumatic chromatolysis), acute total disintegration (ghost cells) or acute progressive necrosis, multinucleation of nerve cells (evidence, presumably, of an abortive attempt at regeneration), and, finally, ferrugination (wrongly designated by some as "calcification"), a process by which a dead cell may remain among the living as a mummified relic for many months or years

The occurrence of definite and widespread chromatolytic changes in the nerve cells, which may persist for some time before reversible change takes place, furnishes a possible basis for the persistent psychic residual disturbances which so often follow craniocerebral injury Local changes in nerve cells observed at the margin of regional traumatic injuries of the cerebral cortex not only furnish an explanation of the deficit pictures which result from loss of functioning areas but probably are responsible for residual convulsive seizures The possible physical counterparts of abnormal discharge of electric current responsible for such seizures could not be determined in this study, concerned as it was largely with cases of craniocerebral injury with relatively short periods of survival

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DISTURBANCES IN SLEEP MECHANISM A CLINICOPATHOLOGIC STUDY

III LESIONS AT THE DIENCEPHALIC LEVEL (HYPOTHALAMUS)

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In contrast to the questionable effect of cortical lesions on the sleep mechanism, it is well known that discrete diencephalic lesions, especially in the hypothalamus, are accompanied with disturbances in sleep There is a wealth of clinical and experimental evidence that the hypothalamus acts as a sleep-regulating center Conclusions regarding the relationship of anatomic lesions in the hypothalamus to precise disturbances in function should be made with reservation, because areas adjacent to the hypothalamus, such as the thalamus and the basal ganglia, may also be involved by compression or edema We wish to emphasize that in many of the reported cases, as in some of ours, the lesions were widespread The 17 cases to be described and the recently recorded experimental data of Harrison, Magoun and Ranson[1] may help in the clarification of these intricate problems We shall attempt to demonstrate that in a few of our cases the hypothalamus was involved to the exclusion of the thalamus and the basal ganglia, whereas in most of the other cases such exclusion could not be shown Only in a few of our cases could involvement of specific portions of the hypothalamus be related to disturbances in sleep

REPORT OF CASES

CASE 1.—*Adamantinoma of the third ventricle with involvement and destruction of most of the hypothalamic nuclei Endocrine disturbances hyperthermia, ocular manifestations and insomnia, followed by somnolence Increased intracranial pressure*

S P, a woman aged 45, experienced dimness of vision Within a period of one and a half years she gained 70 pounds (31 8 Kg), she slept poorly and later became drowsy The menopause occurred at the age of 39

Neurologic Examination.—Examination disclosed pallor of the optic disks and sluggish pupillary reactions to light and in accommodation The left palpebral fissure was larger than the right There were bilateral ptosis, palsy of the right third nerve and hyperthermia

Laboratory Data.—The spinal fluid was clear and contained no cells The Pandy reaction was faintly positive, and the initial pressure was 140 mm of water The basal metabolic rate, determined on two occasions, was — 13 and — 17 per cent The blood chemistry was normal

Autopsy.—Two small adamantinomas replaced the floor of the third ventricle (fig 1) The entire hypothalamic region was studied serially Practically all the nerve cells of the hypothalamic nuclei in the preoptic, supraoptic and infundibular regions, especially on the right side, were destroyed and showed all types of pathologic changes The nuclear masses involved were the medial and lateral preoptic areas, the lateral hypothalamic area, the lateral tuberal nuclei, the right nucleus supraopticus, nucleus paraventricularis, nucleus suprachiasmaticus, nucleus supraopticus diffusus, nucleus hypothalamicus ventromedialis and nucleus hypothalamicus dorsomedialis, the anterior and dorsal hypothalamic areas and the perifornical area The visible ganglion cells of the various hypothalamic nuclei showed absence of pigment and chromatin granules, homogenization or complete destruction The nerve cells in the mamillary nuclei appeared normal The thalamus and the basal ganglia, except for the left corpus Luysi, were normal

Comment.—The insomnia, followed by drowsiness, was undoubtedly the result of partial destruction of the anterior and posterior hypothalamic nuclei by the adamantinoma It seems

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A report on the study, of which the present paper is the third section, was made before the Chicago Neurological Society on May 20, 1943, and before the New York Academy of Medicine, Section of Neurology and Psychiatry, on Feb 8, 1944 An abstract of the paper, with discussion, appeared in the January 1945 issue of the ARCHIVES, page 79

1 Harrison, F, Magoun, H W, and Ranson, S W Some Determinations of Thresholds to Stimulation with Faradic and Direct Current in the Brain Stem, Am J Physiol **121** 708, 1938

reasonable to assume that the initial symptoms of insomnia were caused by the lesions in the rostral hypothalamic region Later, with involvement of the caudal portion of the hypothalamus, somnolence appeared There were also some ocular manifestations, such as bilateral ptosis and paralysis of the right third nerve The dilated ventricles were considered the result of increased intracranial pressure

CASE 2[2]—*Angioma of the hypothalamus, extending from the rostral part of the supraoptic region to the mamillary bodies Polyuria, polydipsia, hypothermia endocrine disturbance, ocular manifestations and somnolence Increased intracranial pressure*

M R, a man aged 31, had suffered bilateral progressive loss of vision, this condition had gradually improved During the past thirteen years he had slept a great deal and was drowsy most of the day but could easily be awakened

Neurologic Examination—Examination disclosed bilateral anosmia, atrophy of the optic nerves and left homonymous hemianopsia Convergence was defective in the left eye The left palpebral fissure was wider than the right During his stay in the hospital the patient had a consistently low temperature, ranging from 97 6 to 90 F, and slept most of the time

Laboratory Data—The cholesterol of the blood measured 177 mg and the urea nitrogen 9 9 mg, per hundred cubic centimeters The spinal fluid was clear and under an initial pressure of 180 mm of water Tests for globulin gave a slightly positive reaction The urine was normal The basal metabolic rate, determined at various periods, was —36, —43 and —23 per cent

Autopsy—There was a tumor between the floor of the third ventricle and the sella turcica, extending from the optic nerves to the mamillary bodies (fig 2) Practically the entire floor of the third ventricle was destroyed by the neoplasm Serial sections through various hypothalamic regions revealed that most of the nerve cells of the hypothalamic nuclei had undergone pathologic changes This was especially true in sections through the nuclei in the supraoptic and infundibular regions In the mamillary region, the supramamillary area, the medial and lateral mamillary nuclei, the lateral hypothalamic area, the nucleus intercalatus and part of the substantia grisea centralis were destroyed The right mamillary body was more involved than the left (fig 2 *E*) The thalamus and the basal ganglia appeared normal

Comment—Although the entire hypothalamus was involved, the hypersomnia was apparently secondary to destruction of the caudal part of the hypothalamus, affecting the lateral hypothalamic nuclei in that region

CASE 3—*Neuroblastoma of the most caudal part of the hypothalamus and the aqueduct of Sylvius Endocrine disturbances, hypothermia, ocular manifestations and reversal in sleep mechanism Increased intracranial pressure*

B M, a woman aged 23, gave a history of gain in weight, tendency to hirsutism, attacks of vertigo and falling, blindness in the right eye and diminished vision in the left eye

Neurologic Examination—Examination disclosed bilateral secondary atrophy of the optic nerve, dilatation of the pupils, the left being larger than the right, with absence of the reaction to light but with a slight reaction on convergence, incomplete ptosis on the left side, and partial ptosis on the right, slight bilateral weakness of the external rectus muscle, failure of convergence of the right eye, and impairment of upward gaze of the left eye The patient slept poorly, was inattentive and frequently rubbed and scratched her nose During the day

Fig 1 (case 1)—Adamantinoma destroying the floor of the third ventricle and part of the hypothalamic nuclei

she was frequently drowsy and slept but could be aroused At night she was unable to sleep In addition, she had hypothermia

Laboratory Data—The urine showed a faint trace of albumin The blood pressure was 112 systolic and 80 diastolic The blood chemistry was normal The spinal fluid was clear and contained 1 cell per cubic millimeter The Pandy reaction was negative The initial pressure was 360 mm of water

Autopsy—A section through the most caudal part of the third ventricle revealed a neuroblastoma which impinged on the posterior wall of the left side of the third

2 This case was described in detail from the point of view of disturbances in temperature in a previous publication (Davison, C, and Selby, N E Hypothermia in Cases of Hypothalamic Lesions, Arch Neurol & Psychiat **33** 570 [March] 1935)

ventricle, close to the aqueduct of Sylvius (fig 3) The latter was constricted and obstructed by the tumor (fig 3) The hypothalamus and the mesencephalon were studied serially Sections through the preoptic, lateral supraoptic and infundibular regions of the hypothalamus were normal except for congestion of the vessels Occasional ischemic changes and chromatolysis were present in the nerve cells of the lateral hypothalamic area of the caudal infundibular region A section through the most caudal part of the mamillary region disclosed extensive destruction and pathologic changes in the nerve cells of the lateral mamillary nuclei and the lateral hypothalamic area, particularly on the left side The thalamus and the basal ganglia were normal

Fig 2 (case 2) —Coronal sections of the brain *A,* section through the preoptic region, showing a tumor invading the right side only, *B,* section through the rostral part of the supraoptic region, showing the tumor invading the oral part of the paraventricular nucleus, *C,* section through the beginning of the infundibular region, showing the tumor invading and destroying the ventromedial, tuberal, supraoptic and lateral hypothalamic nuclei, *D,* section through the middle of the infundibular region, showing the tumor invading and destroying the tractus supraopticus and ventromedial part of the posterior, dorsal and lateral hypothalamic areas, *E,* section through the anterior part of the mamillary region, showing the tumor invading and destroying the nerve cells of the nuclei intercalatus, the nuclei mamillaris medialis and lateralis, the supramamillary area, the right fasciculus mamillothalamicus and the lateral hypothalamic area, and *F,* section through the posterior part of the mamillary region The mamillary bodies could be identified at this level, there is destruction of the right mamillary body The nerve cells of the mamillary nuclei and the lateral hypothalamic areas showed pathologic changes at this level

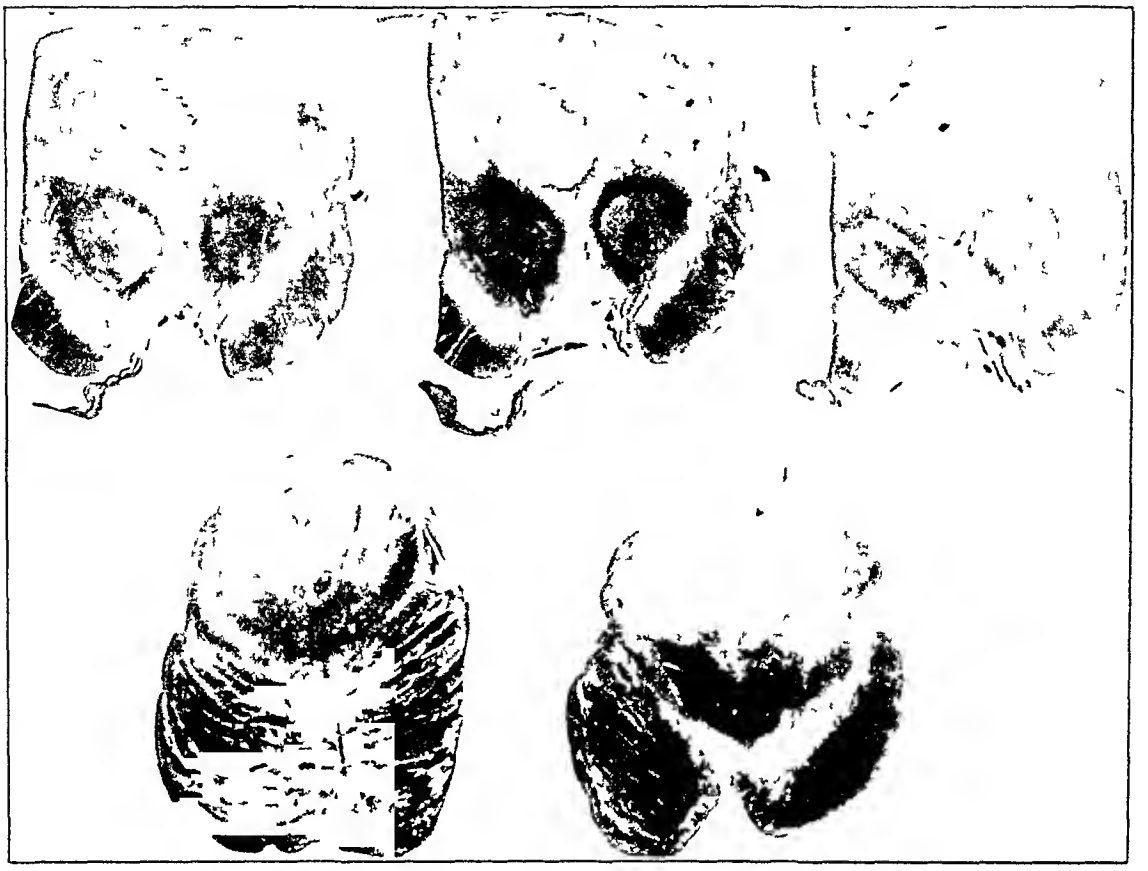

Fig 3 (case 3) —Neuroblastoma of the caudal end of the hypothalamus and the rostral part of the mesencephalon

Fig 4 (case 4) —Colloid tumor of the third ventricle, compression of the hypothalamus

Comment —The disturbance in sleep mechanism was undoubtedly the result of involvement of the caudal region of the hypothalamus Additional points of interest in this case were the reversal of sleep rhythm and the involvement of the nuclei of the ocular nerves

Case 4 —*Colloid tumor of the third ventricle, compression and partial destruction of the hypothalamus,*

especially the anterior and middle thirds, somnolence Increased intracranial pressure

M J, a girl aged 9 years, suffered from frontal headaches and lethargy, from which she could be aroused

Neurologic Examination—There were lateral deviation of the eyes, absence of the knee jerk and a bilateral Babinski sign The patient died a few hours after a spinal tap

Laboratory Data—The spinal fluid was stated to be under slightly increased pressure, there were traces of globulin and 67 lymphocytes per cubic millimeter

CASE 5—*Carcinoma of the lung with metastases to the hypothalamus, thalamus and cerebral peduncle on the left side Hemiplegia oculomotorius alternans, somnolence Increased intracranial pressure*

R L, a woman aged 39, had a carcinoma of the lung Eight months after appearance of the pulmonary signs, there developed paralysis of the right side of the body, blurring of vision, drooping of the left lid, right internal strabismus and attacks of somnolence, from which she could be aroused

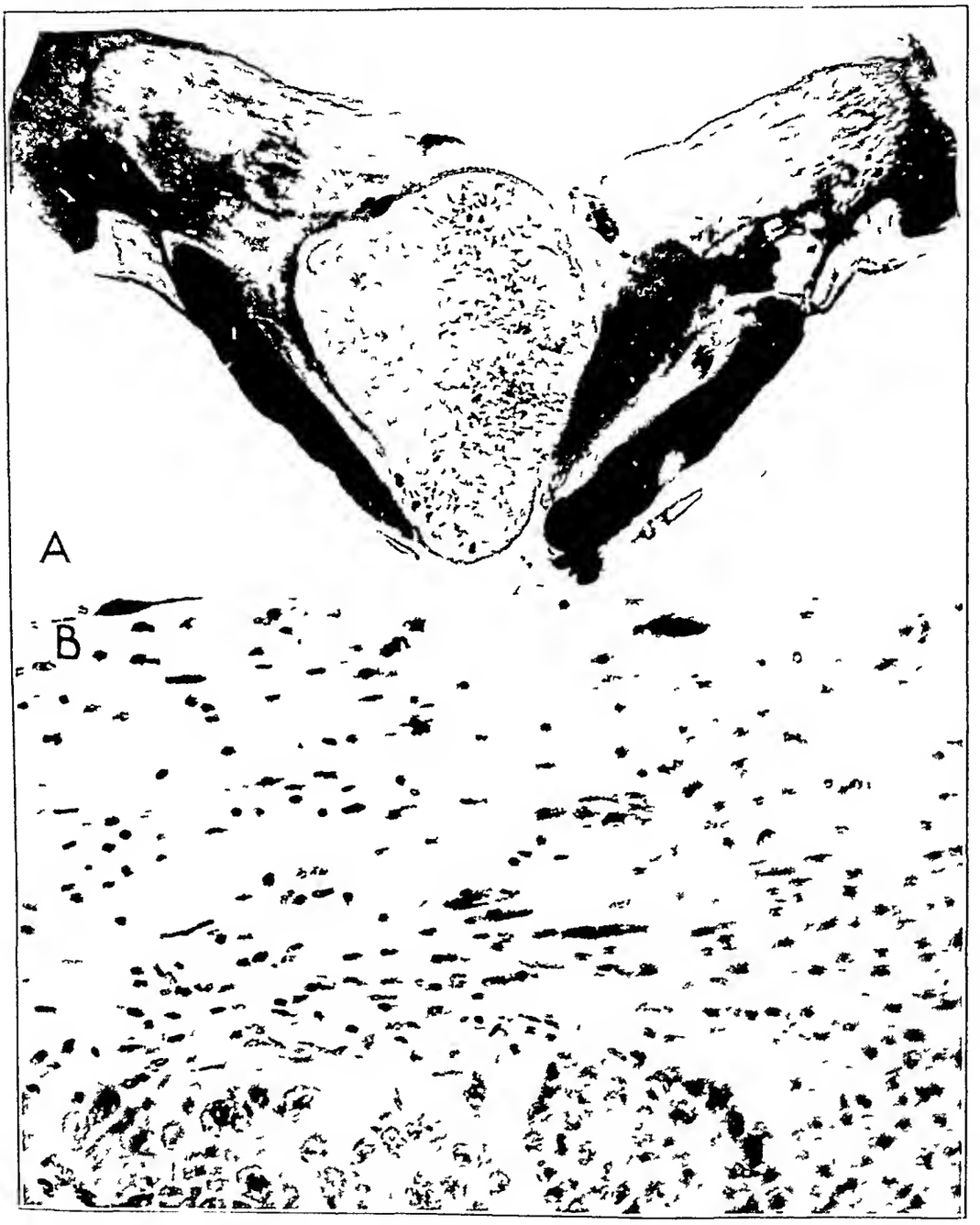

FIG 5 (case 5)—*A*, metastatic carcinoma in the caudal part of the left hypothalamus, with compression of the right hypothalamus, *B*, diminution in number, extreme shrinkage and pyknosis of the hypothalamic nerve cells

Autopsy—A colloid tumor filled the slightly dilated third ventricle and compressed the hypothalamic nuclei (fig 4) The various nerve cells of the hypothalamus, especially in the anterior and middle thirds, disclosed shrinkage, chromatolysis, disappearance of pigment granules and occasional pyknosis Although the posterior part of the hypothalamus was free from tumor, the nerve cells showed loss of chromatin and iron pigment with occasional disintegration

Neurologic Examination—Examination disclosed flaccid hemiparesis with hyperreflexia and pathologic reflexes on the right side, paralysis of the left third nerve, paralysis of upward gaze, and paralysis of the right side of the face of central type The right pupil was smaller than the left

Laboratory Data—Studies of the spinal fluid were not recorded The urine and the blood chemistry were normal

Autopsy—A metastatic tumor in the left caudal hypothalamic region (fig 5*A*) compressed the medial nucleus of the thalamus, the substantia nigra, the corpus Luysi, the cerebral peduncle and the third nerve on that side (fig 5*A*) The tumor also extended into the mesencephalon as far as the superior part of the fourth ventricle The posterior third of the left hypothalamus was almost completely destroyed The surviving nerve cells showed all types of pathologic changes, such as diminution, shrinkage and pyknosis (fig 5*B*) The nerve cells of the right hypothalamic nuclei exhibited ischemic changes and chromatolysis

Comment—This case presented the classic picture of Weber's syndrome and somnolence as a result of invasion of the posterior part of the hypothalamus by the tumor The influence of the thalamus and the basal ganglia cannot be completely ruled out because of compression

CASE 6—*Meningioma of the base of the brain, invading the caudal part of the left hypothalamus, with compression and destruction of the right hypothalamus Ocular manifestations, hyperthermia and somnolence No evidence of increased intracranial pressure*

B S, a man aged 52, had so-called influenza for ten days, associated with fever during that period, followed by lethargy, drowsiness and stupor, from which he could be aroused

Fig 6 (case 6)—Meningioma invading the caudal portion of the left hypothalamus and compressing the diencephalon Notice also the compression of the opposite hypothalamus

Neurologic Examination—Examination revealed pathologic laughing and crying, spastic right hemiplegia, parkinsonian facies and sluggish pupillary responses to light and in accommodation Lack of convergence, impairment of movements on upward, downward and lateral gaze, nystagmus and paresis of the right side of the face of central type were also present

Laboratory Data—Spinal tap revealed a normal status, pressure readings could not be carried out successfully because of the forced laughing and crying The urine and the blood chemistry were normal

Autopsy—A meningioma was found at the base of the brain between the left hippocampus and the left peduncle (fig 6) The tumor invaded and compressed the following structures on the left side the hypothalamus, the inferior parts of the medial and lateral thalamic nuclei, the corpus Luysi, the substantia nigra, the cerebral peduncle and the mamillary body (fig 6*A*) Practically the entire left side of the mesencephalon was compressed in the region of the aqueduct Sections through the supraoptic region showed destruction of the left nucleus supraopticus, part of the left paraventricular nucleus and the left lateral and anterior hypothalamic areas, with pathologic changes in the nerve cells In sections through the posterior part of the third ventricle, the tumor invaded and destroyed the greater part of the ventromedial and dorsomedial hypothalamic nuclei on the left side and the lateral, dorsal and posterior hypothalamic areas, the mamillary nuclei and the nucleus intercalatus on the same side (fig 6*B*) The nerve cells of these masses on the left side showed pathologic changes, but those on the right side were normal In sections through the aqueductal region, there were distortion and compression of the aqueduct, with destruction of part of the left pulvinar and part of the mesencephalon

Comment—The extension of the tumor into the caudal part of the left hypothalamus undoubtedly resulted in lethargy The role played by other involved hypothalamic areas and the compression of the thalamus and basal ganglia in sleep dysfunction cannot be ruled out

CASE 7—*Meningioma at the base of the brain, compression of and hemorrhages into the hypothalamus Insomnia followed by somnolence Increased intracranial pressure*

G M, a man aged 44, had complained of insomnia, vertigo, diminished vision and olfactory hallucinations for four years

Neurologic Examination—Examination revealed bilateral anosmia, irregular pupils, poor ocular convergence and generalized hyporeflexia One week after admission the patient became drowsy and dull On being aroused, he was able to concentrate for only a short time before relapsing into sleep At times there were periods of hyperactivity, alternating with sleepiness At operation a large meningioma was removed from the base of the brain The patient died the same day

Laboratory Data—The cerebrospinal fluid showed an initial pressure of 280 mm of water and 108 mg of protein per hundred cubic centimeters The urine and blood were normal The nonprotein nitrogen of the blood measured 31 mg per hundred cubic centimeters

Autopsy—There was a large excavation in the orbital surface of the right frontal lobe from removal of the tumor Small hemorrhages, with decomposition of red cells, were found in the internal capsule, the striatum and the posterior hypothalamic nuclei on the right side There were numerous avascular areas in which the nerve and glia cells of the hypothalamus had disappeared, while other nerve cells disclosed extensive changes, disintegration, chromatolysis and disappearance of Nissl substance

Comment—The sleepiness in this case must have resulted from the hemorrhages in the posterior part of the hypothalamus These hemorrhages were present prior to the operation, as they showed evidence of decomposition of red cells The insomnia which preceded the somnolence may have been caused by compression of the anterior part of the hypothalamus The involvement of the basal ganglia and their influence on disturbance of sleep cannot be ruled out

CASE 8—*Adenoma of the pituitary gland with compression and invasion of the hypothalamus Insomnia later replaced by short periods of drowsiness Increased intracranial pressure*

L G, a boy aged 8 years, had daily attacks of projectile vomiting, restlessness and insomnia A month later he experienced frontal headaches, dizziness, poor vision and attacks of drowsiness, lasting one to several minutes, during which time he would appear as though in a trance He could always be aroused

Neurologic Examination—Examination disclosed bilateral papilledema, atrophy of the optic nerves, irregularity of the pupils, with sluggish reaction to light, areflexia, a bilateral Babinski sign, and nuchal rigidity Studies of the spinal fluid were not recorded

Autopsy—An adenoma of the pituitary projected into the circle of Willis, compressing all its vessels, the optic nerves, chiasm and tracts, the third and sixth nerves and the floor of the third ventricle (figure 7) Part of the neoplasm actually invaded the hypothalamus The nerve cells of the various hypothalamic nuclei, especially in the infundibular region, showed all types of pathologic changes, such as disintegration, chromatolysis, loss of iron pigment or a shadow-like appearance The thalamus and the basal ganglia were normal

Comment—This case was of interest because the patient at first suffered from insomnia and later from short periods of drowsiness almost resembling narcolepsy There were invasion and compression of the entire hypothalamus

CASE 9—*Adenoma of the pituitary gland with compression of and pathologic changes in the hypothalamic nerve cells Somnolence Increased intracranial pressure*

L O, a woman aged 50, complained of drowsiness and fatigue in the early evening

Neurologic Examination—Examination revealed mental hebetude, hypertension, hyperglycemia and primary atrophy of the optic nerve bilaterally The left pupil reacted to light but not in accommodation There was paralysis of the left sixth nerve

Laboratory Data—The blood urea nitrogen varied from 22 to 40 mg, and the blood sugar at times was increased to 220 mg per hundred cubic centimeters The cerebrospinal fluid was not studied

Autopsy—A large tumor of the pituitary gland between the two cerebral peduncles compressed the floor

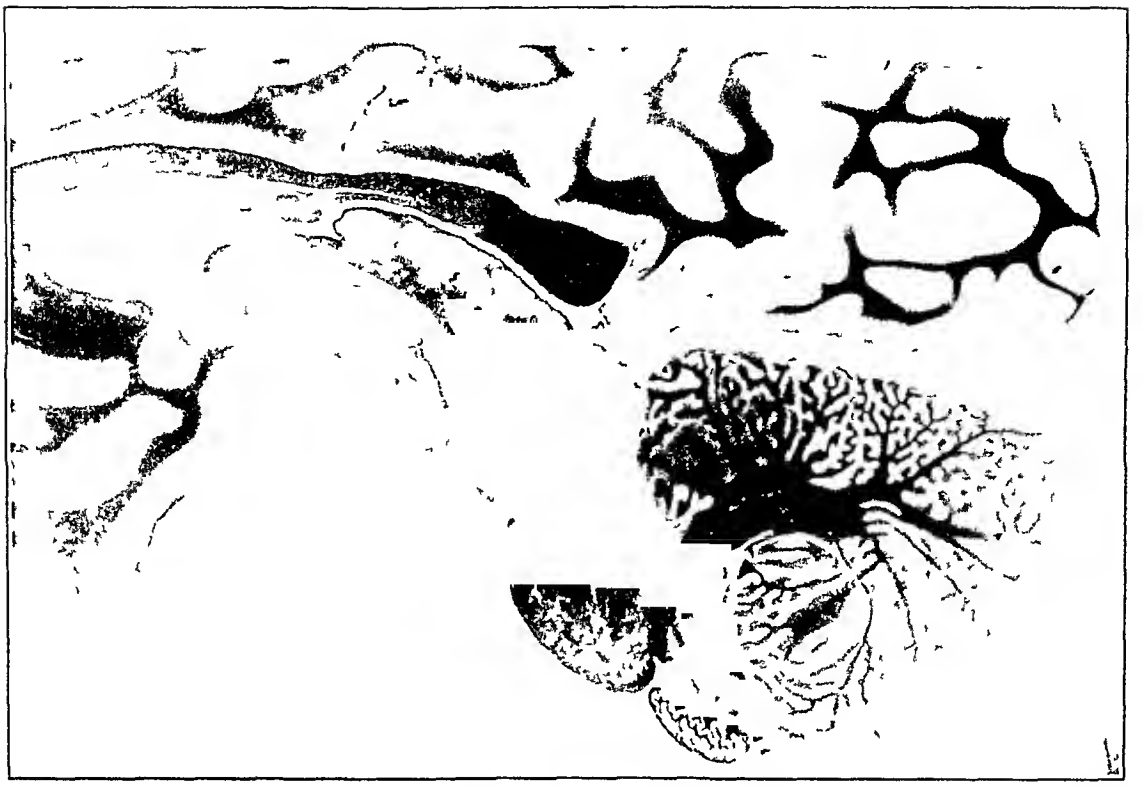

Fig 7 (case 8) —Adenoma of the pituitary gland, with invasion and compression of the hypothalamus

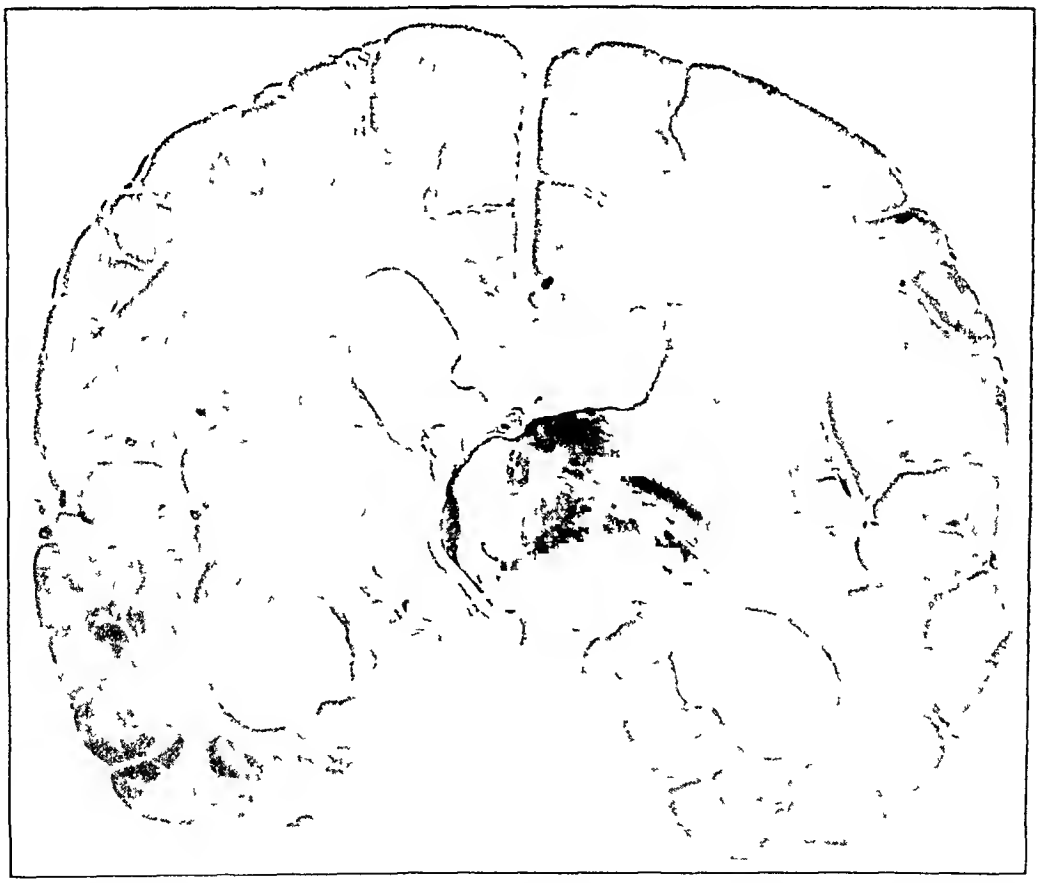

Fig 8 (case 10) —Glioblastoma multiforme of the right hypothalamus and the right side of the diencephalon Note the compression of the opposite hypothalamus

of the third ventricle and the hypothalamus The various hypothalamic nerve cells, both anteriorly and posteriorly, showed pathologic changes, such as loss in Nissl substance, shrinkage, pyknosis and loss of iron pigment The thalamus and the basal ganglia were normal

CASE 10—*Glioblastoma multiforme of the right diencephalon, with unilateral invasion of the hypothalamus but with bilateral pathologic changes, more pronounced on the right side Drowsiness, stupor Increased intracranial pressure*

S L, a man aged 60, became drowsy and dozed off frequently for short periods during the day He became careless about his appearance and lost interest in his surroundings

Neurologic Examination—The patient was stuporous He responded with grimaces to painful stimuli and could be awakened with difficulty There were bilateral papilledema, conjugate deviation of the eyes to the right, mimetic palsy of the left side of the face, hyporeflexia, tremors and coarse involuntary movements of the upper extremities Studies of the spinal fluid were not recorded

Autopsy—A large tumor destroyed the following structures on the right side the inferior part of the internal capsule, the thalamic nuclei and the middle and caudal portions of the hypothalamus The right striatum and pallidum and the left hypothalamus were compressed (fig 8) The remaining hypothalamic nerve cells on the right side were either completely destroyed or showed marked pathologic change The nerve cells of the left hypothalamus showed loss of Nissl substance and heavy granules of iron pigment

Comment—Drowsiness in this case could be explained on the basis of involvement of the caudal part of the hypothalamus The thalamohypothalamic and striohypothalamic pathways may also have played a role in this dysfunction

CASE 11—*Glioblastoma multiforme of the left temporal lobe with metastases to the hypothalamus, involving essentially the infundibular and mamillary regions Hyperthermia, ocular manifestations and somnolence Increased intracranial pressure*

FIG 9 (case 11)—Glioblastoma multiforme with metastases to the hypothalamus, involving essentially the infundibular and mamillary regions (*A*, myelin sheath stain, *B*, cresyl violet stain)

S A, a man aged 31, had a glioblastoma multiforme in the left temporofrontal region, the tumor has been partially removed After a second operation hyperthermia developed Five months later the patient began to have projectile vomiting, headaches and drowsiness, from which he could be aroused At this time there was marked hypothermia The right pupil did not respond to light or in accommodation, and there was weakness of the left lateral rectus muscle

Laboratory Data—The blood chemistry was normal The spinal fluid was clear, contained 75 mg of protein per hundred cubic centimeters and showed an initial pressure of 200 mm of water

Autopsy—The third frontal and the temporal convolutions on the left side were the seat of a neoplasm The tumor invaded the rostral, middle and caudal hypo-

thalamic nuclei (fig 9) The greatest involvement was in the medial wall of the middle and caudal portions of the hypothalamus Most of the nerve cells of the supraoptic and lateral hypothalamic areas were well preserved There were compression and edema of the thalamus and the basal ganglia on the right side

Comment—The patient's drowsiness during the past month and the hypothermia were undoubtedly caused by the neoplastic invasion of the caudal part of the lateral hypothalamic areas where the destructive process seemed most advanced The lethargy in this instance did not appear until the tumor invaded the hypothalamus The involvement of the thalamus and the basal ganglia may also have played a role in the somnolence

CASE 12—*Glioblastoma multiforme involving the posterior part of the hypothalamus, pulvinar and mesencephalon Insomnia, followed by somnolence No evidence of increased intracranial pressure*

T I, a man aged 58, first experienced insomnia and later somnolence, from which he could be aroused

Neurologic Examination—There were a left hemisensory syndrome and bilaterally diminished hearing

Laboratory Data—The blood chemistry was normal The spinal fluid was clear and contained 1 cell per cubic millimeter and 62 mg of protein per hundred cubic centimeters, the initial pressure was 144 mm of water

Autopsy—There was a tumor in the region of the pulvinar, the thalamic nuclei and the hypothalamus on the right side, with compression of the posterior part of the opposite side of the hypothalamus and the mesencephalon Other discrete masses on the right side were present in the thalamic nuclei, the peduncle close to the external geniculate body and the white matter near the temporal lobe and the island of Reil Some of the fibers of the internal capsule were involved In sections through the pons, the tumor involved the nuclei of the third and fourth cranial nerves and the posterior longitudinal bundle The nerve cells of the posterior part of the hypothalamus showed all types of pathologic changes, such as diminution, shrinkage, chromatolysis and complete destruction

Comment—The tumor in this instance was essentially situated in the caudal hypothalamic region and the thalamus and mesencephalon Clinically, there was no evidence of involvement of the ocular nerves, pathologically, however, the third and fourth nerve nuclei and the posterior longitudinal bundle were implicated The role played by the thalamus in sleep dysfunction cannot be totally ruled out in this case

CASE 13—*Hemorrhage in the diencephalon and mesencephalon Somnolence Clinical evidence of increased intracranial tension*

H I, a man aged 64, after an emotional upset had an attack of dizziness, blurred vision and diplopia

Neurologic Examination—Examination disclosed signs of involvement of the pyramidal tract and pathologic reflexes on the left, a right hemisensory syndrome and nystagmus on lateral gaze Later the patient became somnolent but could be aroused

Laboratory Data—The blood chemistry was normal Studies of the spinal fluid showed no cells, a negative Pandy reaction, 39 mg of protein per hundred cubic centimeters and an initial pressure of 80 mm of water

Autopsy—A massive hemorrhage on the right side had destroyed the external capsule, the claustrum, the putamen, part of the internal capsule and part of the thalamic and the middle and caudal hypothalamic nuclei (fig 10) The hemorrhage extended into the rostral part of the mesencephalon The nerve cells of the hypothalamic nuclei had a washed-out appearance, with evidence of chromatolysis, ischemia and conspicuous loss of iron pigment

Comment—The somnolence which appeared toward the end of the illness was due to extensive hemorrhages in the diencephalon and the rostral part of the mesencephalon The influence of the thalamus and the basal ganglia on this dysfunction cannot be ruled out

CASE 14—*Encephalitis lethargica Lesions of the basal ganglia and hypothalamus Reversal of sleep mechanism—somnolence during the day and insomnia at night Ocular manifestations No increased intracranial pressure*

O E, a woman aged 20, gave a history of influenza in 1920 and symptoms of asthenia, dizziness, diplopia, drowsiness with excessive sleepiness during the daytime, from which she could be aroused, and insomnia during the night Later, a typical picture of paralysis agitans developed There were periods of amenorrhea during her illness

Neurologic Examination—There was a typical picture of paralysis agitans, the right pupil was greater than the left, and both reacted sluggishly to light There was some disturbance in convergence

Laboratory Data—The blood chemistry was normal The spinal fluid was clear and contained no cells The total protein measured 24 mg per hundred cubic centimeters The pressure was stated to be normal

Autopsy—The pathologic picture of the pallidum and substantia nigra was typical of paralysis agitans, with areas of necrobiosis and calcification of vessels There was also a small area of necrobiosis in the right nucleus supraopticus The ganglion cells of the caudal hypothalamic nuclei stained poorly and did not have the high content of iron generally seen

Comment—The lethargy in this case was most likely the result of the lesions in the striohypothalamic pathways and the hypothalamus The role played by the basal ganglia cannot be ruled out

CASE 15—*Paralysis agitans Lesions in the basal ganglia and, to a lesser extent, in the hypothalamus Ocular manifestations, somnolence No increased intracranial pressure*

S M, a woman aged 42, had diplopia, drowsiness and then somnolence, lasting five months, from which she could be awakened Lumbar punctures, performed every three months, relieved the hypersomnia for short periods

Neurologic Examination—Examination disclosed a typical picture of paralysis agitans The pupils reacted to light, but there was paralysis of accommodation and convergence The temperature was often 97 F, and terminally it reached 96 F

Laboratory Data—The blood chemistry was normal Spinal puncture disclosed a clear fluid, with no cells

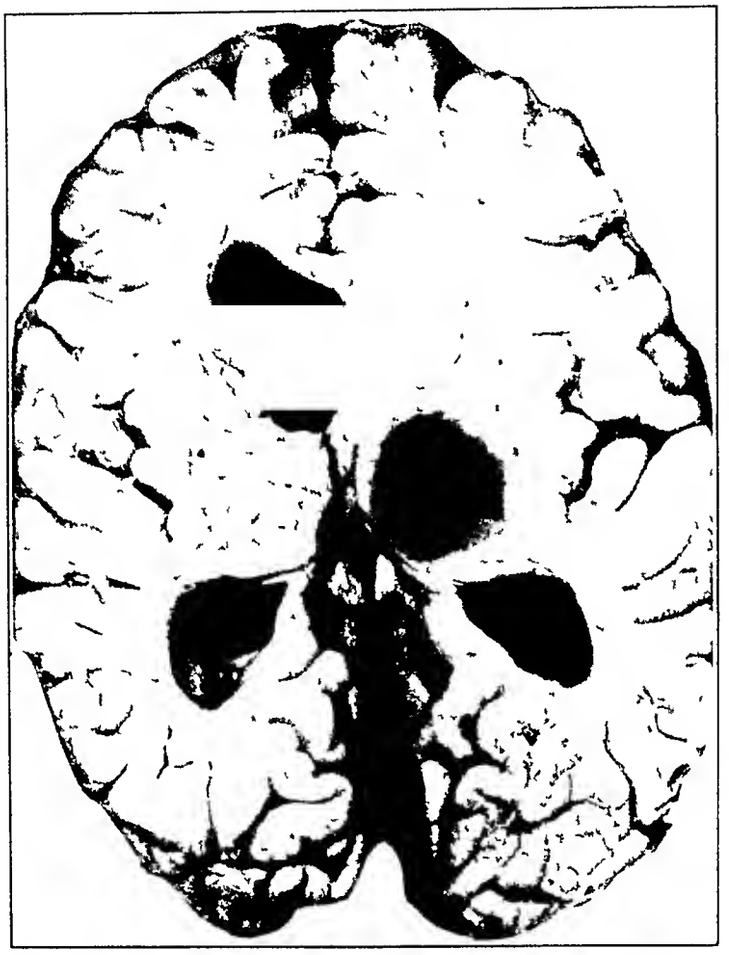

Fig 10 (case 13) —Hemorrhages in the hypothalamus and thalamus

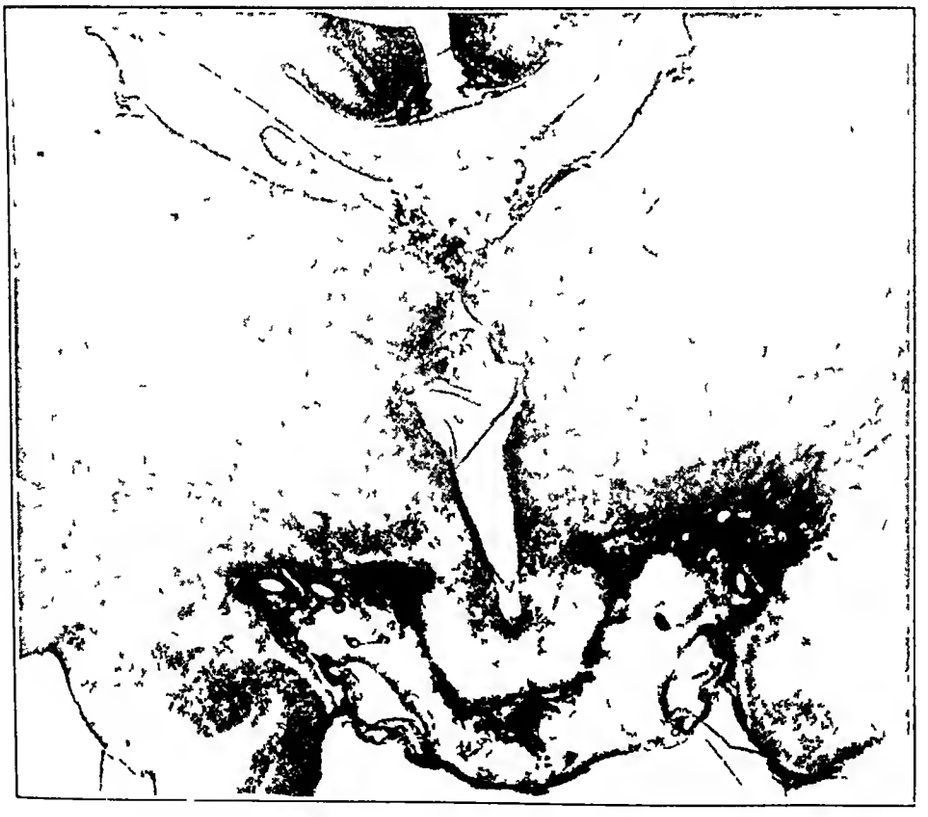

Fig 11 (case 16) —Tuberculous basilar meningitis, invading the hypothalamus

and a total protein content of 19 mg per hundred cubic centimeters Pressure readings were not recorded

Autopsy—The basal ganglia showed the changes typical of paralysis agitans, with extensive involvement of the pallidum and the substantia nigra The hypothalamic nerve cells, especially those of the caudal part, were diminished in number and shrunken and showed lack of pigment granules

Comment—Although this case was placed in the diencephalic group, it is difficult to state with

certainty whether the lethargy was due to the lesion in the hypothalamus or to the involvement of the striohypothalamic pathways

CASE 16.—*Tuberculous basilar meningitis, invasion of the hypothalamus. Somnolence. Increased intracranial pressure.*

D. L. P., a man aged 36, left home in search of work and was found several days later in another city. He complained of being sleepy. He fell asleep while talking and remained in continuous stupor except when strong stimuli were applied.

Neurologic Examination.—The patient was apathetic, disoriented, especially spatially, and somnolent. The temperature was 104 F. Kernig and Brudzinski signs were elicited, and pyramidal tract signs were present bilaterally.

Laboratory Data.—The spinal fluid had an initial pressure of 280 mm. of water and contained 270 cells per cubic millimeter.

Autopsy.—The meninges at the base were extensively thickened and showed evidence of tuberculous meningitis. Part of the inflammatory process extended into the region of the hypothalamus (fig. 11). The various hypothalamic nuclei, especially those in the inferior and caudal parts, disclosed all types of pathologic changes, such as neuronophagia, severe cell changes of Nissl, complete disintegration and loss of pigment granules. The thalamus and the basal ganglia were normal.

CASE 17.—*Torular meningitis, involving especially the base of the brain, with invasion of the hypothalamic nuclei and other diencephalic structures. Insomnia, followed by somnolence. Increased intracranial pressure.*

U. M., a man aged 63, gave a history of falling while walking. He also became lethargic and had a tremor of the upper extremities. Two years prior to this illness he had suffered from insomnia.

Neurologic Examination.—The patient was lethargic, with an attitude of indifference and lack of emotional display. Intention tremor and cogwheel rigidity were present bilaterally. Toward the end of his illness the patient had a decerebrate fit, became deeply stuporous and could not be aroused.

Laboratory Data.—All laboratory tests, including studies of the blood chemistry, gave normal results. The spinal fluid was clear and contained no cells, the Pandy reaction was strongly positive, the total protein was 47 mg. per hundred cubic centimeters, and the initial pressure was 140 mm. of water.

Autopsy.—Extensive torular meningitis involved the optic nerves, chiasm and tracts, the floor of the third ventricle, the basal ganglia, the hypothalamic nuclei and the peduncles. The nerve cells of the various hypothalamic nuclei showed all types of pathologic changes. There was internal hydrocephalus.

Comment.—The somnolence was most likely the result of implication of the hypothalamus and the striohypothalamic pathways. This case is of further interest because of the initial period of insomnia, followed by somnolence in two years.

GENERAL COMMENT

Lesions of the diencephalon, especially in the hypothalamic region, are well known to be the most frequent cause of disturbances of sleep.

Mauthner,[3] in 1890, postulated a sleep-regulating center in the periventricular gray matter. He expressed the opinion that this center influenced the passage of impulses to and from the cortex via the thalamus. Later, von Economo,[4] on the basis of his studies on lethargic encephalitis, stated the belief that this center extended in the anteroposterior direction from the hypothalamus to the mesencephalon and laterally to the basal ganglia. He expressed the opinion that inhibitory influences pass from this region to the cerebrum, on the one hand, and to the midbrain, on the other. He postulated a specific center for insomnia and another for hypersomnia. The center for insomnia, or wakefulness, he located in the anterior part of the hypothalamus close to the basal ganglia, while the center for hypersomnia, somnolence or lethargy he located in the posterior part of the hypothalamus, extending as far back as the aqueduct of Sylvius and implicating the nuclei of the ocular nerves. He distinguished between "brain sleep" and "body sleep." The former, he asserted, was the result of inhibitory influences on the thalamus and cortex, while the latter was due to inhibition of the hypothalamic centers. Many investigators (Potzl,[5] Lesniowski,[6] Jacarelli,[7] Tsutsui,[8] Pette[9] and others) accepted this point of view. Potzl,[5] however, attempted to place the center more posteriorly, in the region of the nuclei of the posterior longitudinal bundle, while Pette[9] expressed the belief that there is a close connection between these centers and the endocrine system. Sklhar[10] stated that the periventricular gray matter acts as an inhibitory center on the cerebral cortex, while Retif[11] asserted that there is a reciprocal inhibition between the mesencephalic centers and the cere-

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5 Potzl, O. Zur Topographie der Schlaftzentren. Monatschr. f. Psychiat. u. Neurol. **64**: 1, 1927.

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7 Jacarelli, E. I disturbi del sonno nelle lesioni del mesencefalo, Policlinico (sez. med.) **39**: 452, 1932.

8 Tsutsui, H. Ein Beitrag zur Pathophysiologie des Mittel- und Zwischenhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**: 717, 1937.

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11 Retif, E. Le sommeil dissocie, auto-observation, Rev. neurol. **1**: 880, 1927.

bral cortex Marinesco, Sager and Kreindler [12] and others stated the opinion that sleep is not controlled by a single center but is the result of action of a system of centers, in which the endocrine component acts as a sensitizer of the vegetative centers They also concluded that sleep is a combination of conditioned and unconditioned reflexes Adie,[13] on the basis of evidence derived from cases of narcolepsy, favored an endocrine-neural mechanism located in the floor of the diencephalon, in and around the vegetative centers forming the hypophysial-diencephalic system

Other authors, while of the opinion that the diencephalon acts as a sleep center, stated the belief that the thalamus is the important regulating center (Inaba,[14] Tromner,[15] Hirsch,[16] Lucksch,[17] Brailovsky,[18] Salmon,[19] Spiegel [20] and others) Tromner stated that the thalamus is the only structure to inhibit cortical centers and to regulate the action of the intrinsic and extrinsic ocular muscles and other functions attributed to the hypothalamus He asserted that the thalamus influences hypothalamic centers and that disturbances in sleep can be produced only by bilateral lesions in the thalamus Ranson [21] failed to produce somnolence in several monkeys with extensive bilateral lesions of the thalamus Harrison [22] induced somnolence with passage of a destructive current through the thalamus in cats but was not certain that this action was due to the thalamus alone Stimulation of the thalamus, however, by Mussen [23], Kabat, Anson, Magoun and Ranson,[24] and Harrison,[22] did not result in disturbances in sleep

There are numerous clinicopathologic contributions describing disturbances of sleep as a result of lesions in the diencephalic region (Fulton and Bailey,[25] Lucksch,[17] Hirsch,[16] Strauss and Globus,[26] Lhermitte and Tournay,[27] Adie,[13] Adler,[28] Rowe,[29] Cox,[30] Engel and Aring [31] and others) In some of the cases previously reported, as in some of ours, the lesions were widespread and frequently associated with compression or edema of adjacent areas

The oculomotor phenomena observed in cases of encephalitis in connection with somnolence have been emphasized by some observers as an indication that the sleep center is situated in the vicinity of the aqueduct, the seat of most of the nuclei of the oculomotor nerves (Frank,[32] von Stockert,[33] Kahn [34] and others) Postulation of localization on this basis alone must be accepted with reservation The ocular manifestations in cases with neoplasms are undoubtedly secondary effects resulting from compres-

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21 Ranson, S W Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch Neurol & Psychiat **41** 1 (Jan) 1939

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24 Kabat, H, Anson, B J, Magoun, H W, and Ranson, S W Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am J Physiol **112** 214, 1935

25 Fulton, J F, and Bailey, P Tumors in the Region of the Third Ventricle Their Diagnosis and Relation to Pathological Sleep, J Nerv & Ment Dis **69** 1, 145 and 261, 1929

26 Strauss, I, and Globus, J H Tumor of the Brain with Disturbance in Temperature Regulation, Arch Neurol & Psychiat **25** 506 (March) 1931

27 Lhermitte, J, and Tournay, A Rapport sur le sommeil normal et pathologique, Rev neurol **1** 751, 1927

28 Adler, E Zur Lokalisation des "Schlafzentrums," Med Klin **20** 1321, 1924

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30 Cox, L B Tumors of the Base of the Brain Their Relation to Pathological Sleep and Other Changes in the Conscious State, M J Australia **1** 742, 1937

31 Engel, G L, and Aring, C D Hypothalamic Attacks with Thalamic Lesion, Arch Neurol & Psychiat **54** 1 (July) 1945

32 Frank, C Intorno alla mia scoperta di due nuclei de mesencefalo dell'uomo ed ulteriori studi sui nuclei oculomotri dei mammiferi, Arch gen di neurol, psichiat e psicoanal **11** 1, 1940

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sion or edema of the tegmentum adjacent to the hypothalamus

In addition to the clinical evidence that the hypothalamus is concerned with the regulation of sleep there are experimental physiologic (lesions and stimulation) and pharmacologic data to substantiate this theory A review of this material will be given in a subsequent publication

On the basis of observation derived from this and from other series of cases, as well as evidence of a neuroanatomic and neurophysiologic character, the following afferent and efferent connections concerned with the sleep mechanism can be postulated

Thalamohypothalamic and Hypothalamothalamic Pathways—The evidence of the existence of such pathways seems to be accepted by all investigators Whether these are afferent or efferent has not been determined They consist of fibers which arise from the medial and midline thalamic nuclei and go to the hypothalamic nuclei There may be connections via the inferior thalamic peduncle with the rostral hypothalamic and the lateral tuberal nuclei Many fibers from the substantia innominata enter the lateral preoptic and hypothalamic areas dorsal to the supraoptic nucleus

Thalamomamillary Fibers—These fibers set up relays of somatic, visceral and sensory impulses from the neopallium to the hypothalamus The impulses from the hypothalamus to the thalamus are mediated via the mamillothalamic tract The mamillothalamic tract most likely serves as a link between the hypothalamus and the cerebral cortex, especially the gyrus cingulus The mamillotegmental tract arises in the mamillary bodies and descends through the central gray matter of the aqueduct, with possible contributions to the tectal and tegmental nuclei

Stria Terminalis—This pathway, which also contains preoptic and hypothalamic components conveys fibers from the amygdaloid nucleus to the hypothalamus

Supraoptic Commissures — According to Papez [35] and others, these structures are afferent systems concerned with the integration of emotional expressions

Striopallido Hypothalamic and Subthalamohypothalamic Connections—Such connections have been reported by many observers, but the evidence is not entirely conclusive

Hypothalamohypophysial Pathway—This well known tract runs from the supraoptic, paraventricular and tuberal nuclei to the neurohypophysis

Intrahypothalamic Pathways—These tracts form connections between the various hypothalamic nuclei

Résumé—Our series includes 17 cases with diencephalic lesions In 8 cases there was a neoplasm of the hypothalamus, in 2 of which the lesion was metastatic In 2 cases a pituitary tumor and in 2 a suprasellar tumor either compressed or invaded the hypothalamus The other cases of lesions of the hypothalamus included 2 of basilar meningitis (1 of torular meningitis), 2 of paralysis agitans following lethargic encephalitis and 1 of hemorrhage within the hypothalamus In 14 of the 17 cases intrahypothalamic lesions were disclosed In 16 cases the caudal part of the lateral hypothalamic area showed changes bilaterally There were only 7 cases of pure hypothalamic lesions without involvement of the thalamic or basal ganglia (cases 1, 2, 3 4, 8, 9 and 16) A correlation between insomnia or somnolence and involvement of specific parts of the hypothalamus could not be definitely established from our series because the caudal portion of the hypothalamus was solely affected only in 1 instance (case 3) Although the caudal part of the hypothalamus was involved in most of the other cases (1, 2, 3, 8, 9 and 16) the anterior and middle parts were also affected This problem becomes even more complicated in the remaining cases in which there was additional implication of the thalamus and the basal ganglia Besides the hypothalamic involvement there was implication of the thalamus in 2 cases (11 and 12) of the thalamus and basal ganglia in 4 cases (3, 5, 6 and 13) and of the basal ganglia in 4 cases (7, 10, 14 and 17) A reversal of the sleep mechanism was present in 2 cases, while in 4 others (1 8 12 and 17) the insomnia was followed by somnolence In these cases both the rostral and the caudal portion of the hypothalamus were diseased It is probable that in some of the cases with insomnia the rostral part of the hypothalamus became affected first Somnolence appeared when the lesion extended into the caudal portion of the hypothalamus Evidence of increased intracranial pressure was present in 13 cases This high incidence of increased intracranial pressure is to be expected in this group, since the third ventricle was obstructed, especially in the cases with neoplasms In 1 case there was no clinical evidence of this phenomenon, but internal hydrocephalus was observed at autopsy In 4 cases (6, 12, 14 and 15) there was no evidence of increased intracranial pressure

35 Papez, J W A Proposed Mechanism of Emotion, Arch Neurol & Psychiat **38** 725 (Oct) 1937

These were 2 cases of paralysis agitans, a case of suprasellar meningioma and a case of glioblastoma multiforme Ocular manifestations, consisting of diplopia, ptosis, defective convergence, paralysis or paresis of the ocular muscles and nystagmus, were present in 14 cases, in 1 case ocular disturbances were not recorded The ocular manifestations were undoubtedly the result of compression or edema of the tegmentum These disturbances were more prevalent in this group than in the cases of cortical or corticodiencephalic lesions because of the proximity of the ocular nerve nuclei to the posterior part of the hypothalamus Endocrine disturbances, such as changes in metabolism, adiposity, adiposogenital dystrophy, early menopause and loss of libido, were present in 4 cases (1, 2, 3 and 14) Deviations in temperature from the normal were present in 9 cases, hypothermia was present in 5 cases and hyperthermia in 4 cases In 1 case hyperthermia was later followed by hypothermia Disturbances in temperature should be expected in this group, as the hypothalamic nuclei are concerned with this mechanism

SUMMARY AND CONCLUSIONS

Of 17 cases of pathologic sleep, there was direct involvement of the hypothalamus in 14 cases In 3 cases there was compression of the hypothalamus with pathologic changes in its nerve cells In 16 cases the caudal part of the lateral hypothalamic area showed changes bilaterally There were, however, only 7 cases with pure hypothalamic involvement In the remaining 10 cases there was also invasion, compression or edema of either the thalamus or the basal ganglia or of both, with implication of the thalamohypothalamic and striohypothalamic pathways

Increased intracranial pressure was present in 13 cases and absent in 4 A high incidence of increased intracranial pressure in this series should be expected, as the neoplasm encroached on the ventricular system

Ocular manifestations, in the form of diplopia, ptosis, defective conjugate deviation, paralysis or paresis of ocular muscles, or nystagmus, were present in 14 cases These symptoms were undoubtedly the result of compression or edema of the nuclei of the ocular nerve or their pathways

Endocrine disturbances were present in 4 cases In all these cases the tumor was situated in the pituitary region or there was compression of the hypophysial duct or gland

Deviations in temperature were present in the form of hypothermia in 5 cases and of hyperthermia in 4 cases

From this series of cases of diencephalic lesions, it may be concluded that damage to the hypothalamus, especially the posterior part of the lateral hypothalamic area and of its various pathways bilaterally, causes somnolence The influence of the thalamus or the basal ganglia on this disturbance cannot be completely ruled out

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DISTURBANCES IN SLEEP MECHANISM A CLINICOPATHOLOGIC STUDY

IV LESIONS AT THE MESENCEPHALOMETENCEPHALIC LEVEL

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Disturbances in sleep mechanism as a result of lesions of the pons and medulla oblongata, although rare, have been reported by a number of observers Some investigators are of the opinion that somnolence in cases of such lesions is caused by involvement of the nuclei of the ocular nerves, which are situated in the mesencephalon and metencephalon They believe that the sleep-regulating center is located in the region of these cranial nerve nuclei and that there is a connection between sleep and the ocular mechanism

In our group of 8 cases, it was possible to demonstrate that the descending hypothalamic pathways in the brain stem were invariably implicated Somnolence in these cases was probably due to the lesions in these pathways Involvement of the nuclei of the ocular nerves was secondary to the specific location of the lesion in the brain stem and most likely played an insignificant role in the disturbance in sleep mechanism

REPORT OF CASES

CASE 1 —*Hemangioblastoma of the cerebellum, changes in the medulla oblongata, including the nerve cells of the vegetative nervous system Nystagmus, periodic lethargic episodes Pathologic evidence of increased intracranial pressure*

C C, a man aged 36, had spells of sleepiness and weakness at the age of 12 years Later, he remembered his head falling forward while he was tuning a piano, followed by a dreamless sleep lasting five to fifteen minutes At the age of 24, the periods of somnolence recurred, and he would have to go to bed because of weakness He had been drowsy and easily fatigued ever since, although he could always be aroused The right eye had been enucleated after a trauma twenty years ago, vision in the left eye progressively diminished and was completely lost thirteen years ago, as a result of Lindau's disease Other symptoms, not mentioned in this presentation, had no bearing on the problem under discussion

Neurologic Examination—Examination revealed bilateral cerebellar signs, nystagmus in all directions, muscular weakness, blindness of the left eye and numerous hemangiomas of the skin

Laboratory Data—There was moderate polycythemia A spinal tap was stated to show normal fluid, without increase in manometric pressure The blood chemistry was normal The temperature throughout the course of the illness was normal

Autopsy—There was uniform internal hydrocephalus The fourth ventricle was filled with a hemangioblastoma, which did not invade any of the cerebellar structures (fig 1) The medulla oblongata, the pons and part of the vermis cerebelli were compressed by the tumor The various nerve cells of the nuclei within the medulla oblongata, including those of the vegetative nervous system, showed all types of pathologic changes, such as shadow-like appearance, disintegration, chromatolysis, shrinkage and pyknosis The nerve cells of the hypothalamus displayed no abnormality except for occasional loss in pigment granules

Comment—In this instance, the tumor was essentially situated in the posterior fossa Although the hypothalamus was not involved, its descending fibers were affected, resulting in somnolence

CASE 2—*Hemangioblastoma of the cerebellum with compression of the metencephalon Ocular manifestations, drowsiness, with inversion of the sleep mechanism Increased intracranial pressure*

B S, a man aged 44, complained that he constantly wanted to sleep He used to sit down and sleep for half an hour, awakening with a terrific headache Thereafter he was frequently noted to be drowsy, and he became increasingly irritable Later there developed an inversion of the sleep mechanism, in that he slept spasmodically during the day and not at all during the night He could be aroused from his sleep Unsteadiness of gait, dysphagia, exophthalmos, diplopia and loss of libido developed

Neurologic Examination—Examination revealed papilledema, nystagmus, hyperesthesia of the right cornea and involvement of the tenth, eleventh and twelfth cranial nerves on the right side

Laboratory Data—The temperature varied between 97 and 98 8 F, and for three days it was down to 96 2 F Chemical studies of the blood gave normal

From the Neuropsychiatric Service and the Neuropathological Laboratory of the Montefiore Hospital and the Neurological Department of the Columbia University College of Physicians and Surgeons

The paper of which this study is part was presented before the Chicago Neurological Society on May 20, 1943 (preliminary report) and before the New York Academy of Medicine, Section of Neurology and Psychiatry, on Feb 8, 1944 An abstract of the paper with discussion appeared in the January 1945 issue of the ARCHIVES, page 79

values The spinal fluid was clear, the reaction for globulin was negative Manometric readings were not recorded

Autopsy—A hemangioblastoma in the right cerebellopontile angle extended from the lower third of the pons to the end of the medulla oblongata There was uniform dilatation of the entire ventricular system The medulla oblongata in the region of the eighth nerve was greatly compressed and distorted (fig 2) The vegetative nerve cells and those of the cranial nerves in the medulla oblongata showed pathologic changes, such as chromatolysis, retrograde degeneration, shrinkage, pyknosis and complete destruction The hypothalamus was normal

fissure was larger than the right There were bilateral horizontal nystagmus with inconstant upward nystagmus, slight weakness of the internal rectus muscles and frequent yawning and hiccuping The patient was consistently sleepy Once the somnolence became profound and was successfully combated with a hypertonic solution of sugar The temperature was often 97 F Four months before death he became comatose and was never aroused thereafter

Laboratory Data—The spinal fluid contained 4 cells per cubic millimeter, the Pandy reaction was positive, the protein measured 139 mg per hundred cubic centimeters, the initial pressure was 240 mm of water The blood chemistry was normal

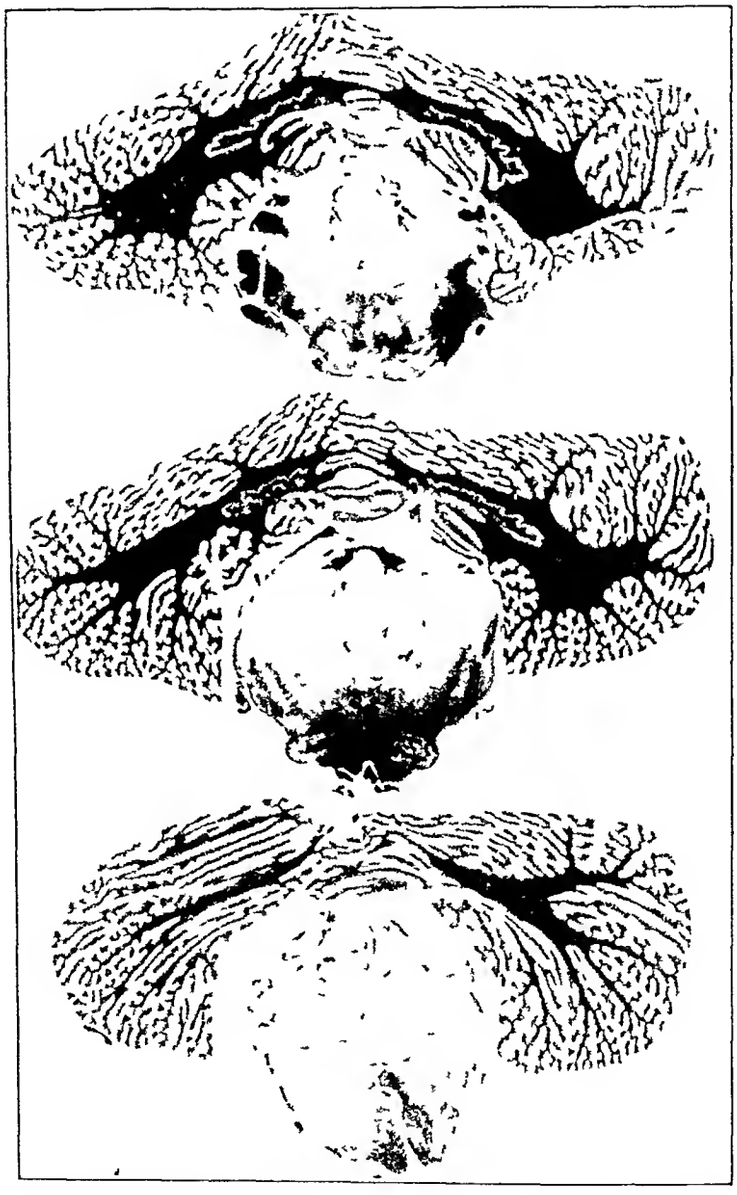

Fig 1 (case 1)—Hemangioblastoma of the cerebellum, compressing the brain stem

CASE 3—*Hemangioblastoma of cerebellum compressing the medulla oblongata Ocular manifestations, drowsiness, followed later by coma Increased intracranial pressure*

A O, a man aged 33, complained of severe frontal headaches, vomiting, diminished vision and dizziness A suboccipital exploration revealed a hemangioblastoma in the region of the fourth ventricle

Neurologic Examination—There were marked drowsiness, from which the patient could be awakened, bilateral cerebellar signs, slight elevation of the disks and fulness of the veins The right pupil was larger than the left, and both reacted well to all stimuli The left palpebral

Autopsy—There was a tumor between the cerebellar vermis and the medulla oblongata, obliterating the fourth ventricle and compressing the mesencephalon and the metencephalon The vegetative nerve cells of the medulla oblongata showed pathologic changes The hypothalamic nuclei did not show any pathologic changes There was tremendous dilatation of the entire ventricular system

CASE 4—*Medulloblastoma of the brain stem, compression of the mesencephalon Ocular manifestations, somnolence Increased intracranial pressure*

G A, a girl aged 16, had dizziness, diplopia, weakness of the extremities, perversion of the sense of touch and somnolence, from which she could be aroused

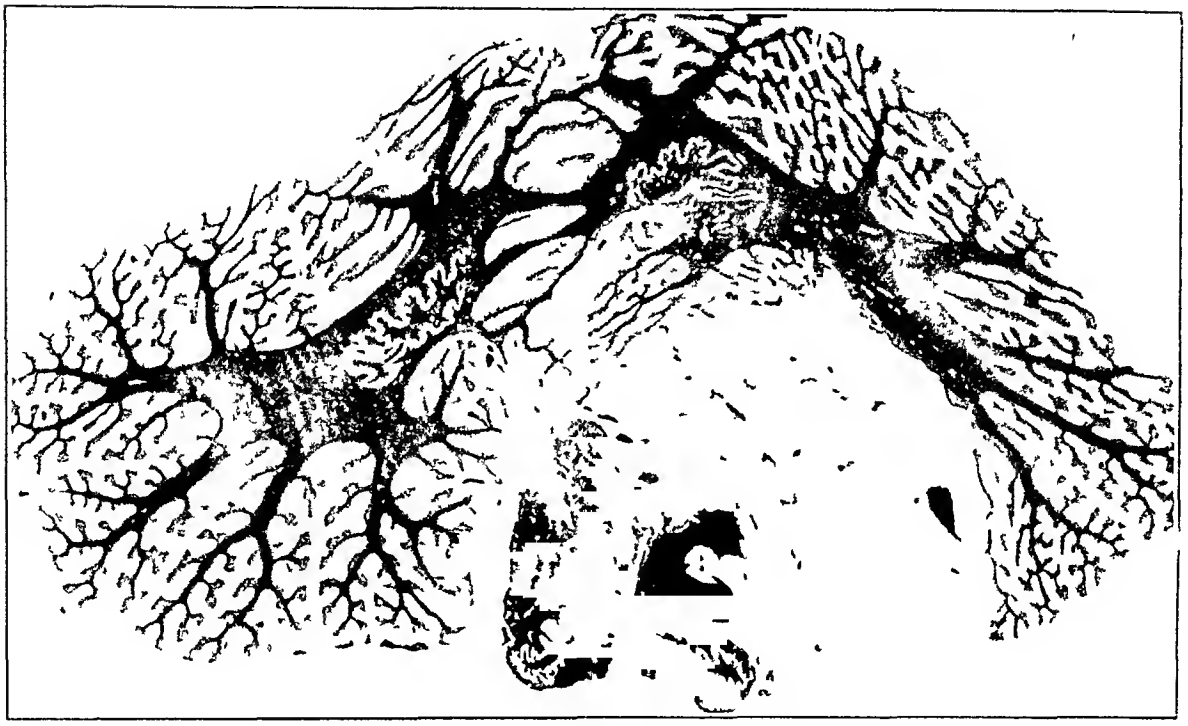

Fig 2 (case 2) —Hemangioblastoma of the cerebellum, compressing and distorting the brain stem

Fig 3 (case 3) —Medulloblastoma of the pons, compressing the mesencephalon, as well as the lower part of the pons

Neurologic Examination.—Examination disclosed cerebellar signs, bilateral signs of involvement of the pyramidal tract, more marked on the right side, impairment of all forms of sensation on the right side of the body, horizontal and vertical nystagmus, some difficulty in horizontal gaze, and papilledema. The patient later manifested bulbar signs, such as dysphagia and dysarthria. She finally became comatose and could not be aroused.

Laboratory Data.—Chemical studies of the urine and blood gave normal values. The spinal fluid was clear, with an initial pressure of 280 mm. of water, and contained 3 cells per cubic millimeter, the Pandy reaction

was negative, and the total protein was 27 mg per hundred cubic centimeters

Autopsy—There was generalized hydrocephalus On the left side of the pons was a medulloblastoma, situated mainly in the pyramid and involving the brachium pontis, the medial lemniscus, the rubrospinal tract, the lateral lemniscus, the nuclei of the sixth and seventh nerves, the vestibular nucleus and Deiters' nucleus (fig 3) The mesencephalon was also compressed The various vegetative nerve cells showed chromatolysis and occasional shrinkage The nerve cells of the hypothalamus were normal

Comment—Although the tumor was essentially situated in the lower portions of the pons, the mesencephalon was compressed, with involvement of some of the hypothalamic pathways and the sympathetic cells

initial pressure of 270 mm of water and a protein content of 147 mg per hundred cubic centimeters

Course—A ventriculogram disclosed symmetric internal hydrocephalus A suboccipital craniotomy revealed no tumor After the operation the patient showed marked somnolence, from which he could be aroused Toward the end the patient became semicomatose but was still able to respond to questioning on stimulation Just before death he had a high fever

Autopsy—There was generalized hydrocephalus A spongioblastoma polare had destroyed the greater part of the tegmentum, the right side being involved more than the left (fig 4) The right pyramid was compressed The following structures were destroyed the superior and inferior colliculi, the brachium conjunctivum, part of the posterior longitudinal bundle, the lateral and part of the medial lemniscus, the descending hypothalamic tract, the various vegetative nerve cells and the nuclei of the fifth and seventh cranial nerves

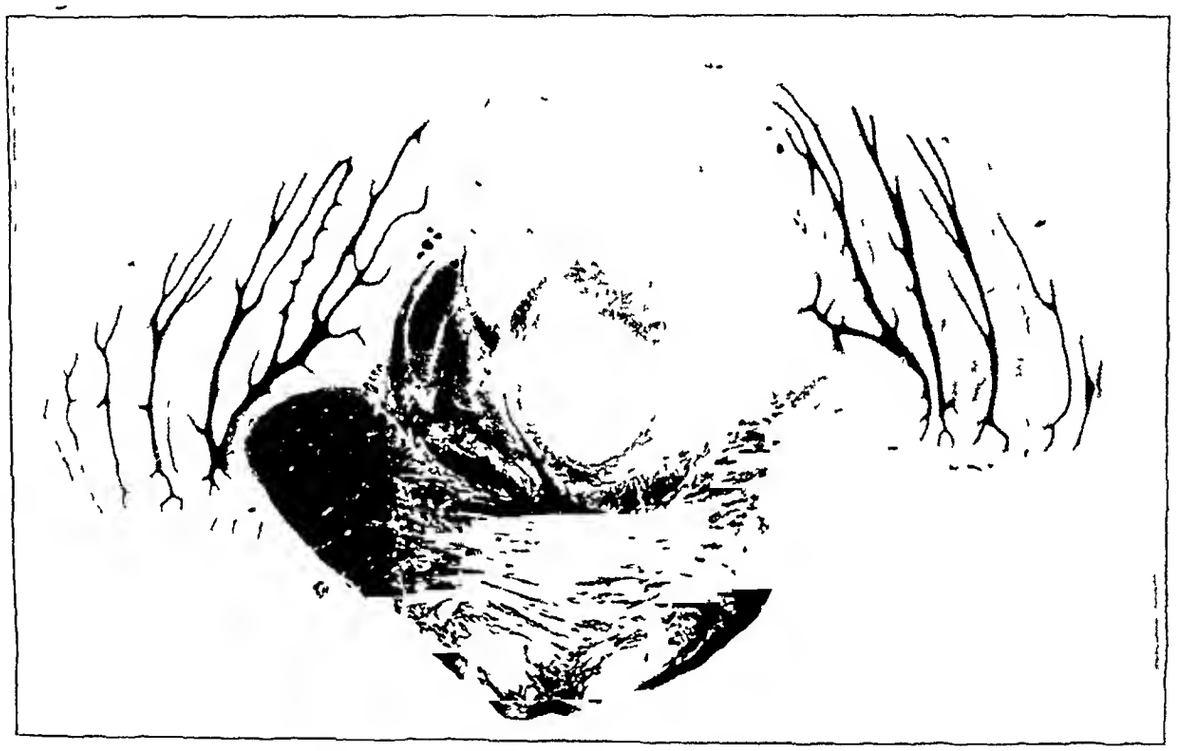

Fig 4 (case 5)—Spongioblastoma polare, destroying the greater part of the right side of the tegmentum Myelin sheath stain

CASE 5—*Spongioblastoma polare of the mesencephalon Ocular manifestations, somnolence Increased intracranial pressure*

S P, a man aged 42, had muscular weakness, diplopia, tinnitus, numbness of the left upper extremity, left hemiparesis and staggering gait, with a tendency to fall to the left

Neurologic Examination—Examination disclosed bilateral cerebellar signs, more pronounced on the left side, signs of involvement of the left pyramidal tract, disturbances in all modalities over the entire left side of the body, papilledema, absence of the left corneal reflex, bilateral convergent squint and bilateral paresis of the sixth nerve, horizontal and rotary nystagmus on lateral and upward gaze, hypesthesia of the left side of the face, palsy of the left facial nerve of peripheral type, and slight diminution in hearing on the left The patient was facetious and somewhat depressed and had lack of insight

Laboratory Data—Chemical studies of the urine and blood gave normal values The spinal fluid showed an

There was compression of the nuclei of the other cranial nerves The nerve cells of the hypothalamus were normal

Comment—The somnolence in this case was undoubtedly the result of the partial destruction of the descending hypothalamic pathways and the vegetative nerve cells in the mesencephalon

CASE 6—*Glioblastoma multiforme of the brain stem Ocular manifestations Lethargy Clinical evidence of increased intracranial pressure*

D L, a boy aged 11 years, complained of dizziness, headache, falling to one side, diplopia and drowsiness, from which he could be awakened

Neurologic Examination—Examination revealed a stuporous condition, ataxia and bilateral signs of involvement of the pyramidal tracts, with pathologic reflexes, the right pupil was larger than the left, and weakness of the left fifth and seventh nerves was noted The

Fig 5 (case 6) —Glioblastoma multiforme of the brain stem

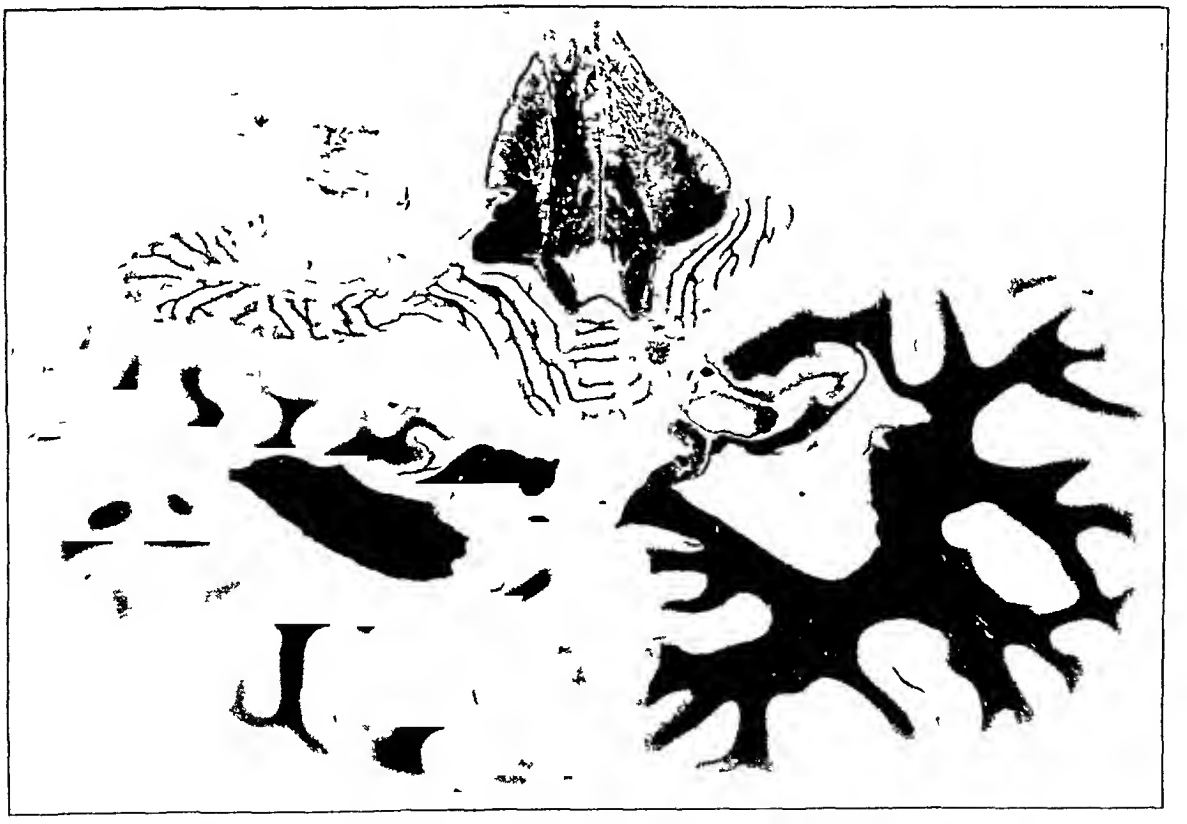

Fig 6 (case 7) —Meningeal fibroblastoma, compressing the brain stem

patient became increasingly drowsy, and there developed papilledema, bilateral ophthalmoplegia and clonic movements of the tongue

Laboratory Data—Spinal tap showed a clear fluid, a cell count of 30 per cubic millimeter and an initial pressure of 80 mm of water The blood chemistry was normal

Autopsy—A large tumor was situated on the right side of the pons, destroying the greater part of it (fig 5) On the right side, the brachium conjunctivum, the posterior longitudinal bundle, the medial and lateral lemnisci and other parts of the mesencephalon were compressed The aqueduct of Sylvius, although distorted, was not obstructed, and there was no ventricular dilatation The nerve cells of the nuclei of the various ocular nerves and of the vegetative nervous system showed pathologic changes The nerve cells of the hypothalamus stained well

Comment—The compression of the descending hypothalamic pathways was probably the cause of the lethargy The increased intracranial tension, as evidenced by the papilledema did not appear until death, whereas the lethargy was present long before this

CASE 7—*Meningeal fibroblastoma of the left cerebellopontile angle with compression of the metencephalon Nystagmus, somnolence Increased intracranial pressure*

S S, a woman aged 58, gave a history of headaches, gradually increasing visual impairment, personality changes and somnolence, from which she could be aroused

Neurologic Examination—Examination disclosed a semistuporous state, from which she could be aroused, pronounced impairment in memory, with limitation of speech and comprehension, spastic quadriplegia, more marked on the right side, with bilateral hyperreflexia and pathologic reflexes, dilated pupils, the right being larger than the left and both responding sluggishly to light, rotary nystagmus and marked secondary atrophy of the optic nerve

Laboratory Data—The blood chemistry was normal A spinal tap disclosed 5 lymphocytes per cubic millimeter, a total protein content of 35 mg per hundred cubic centimeters, and an initial pressure of 220 mm of water

Autopsy—There was a large meningeal fibroblastoma in the left cerebellar hemisphere (fig 6) The entire ventricular system was extensively dilated The medulla oblongata was notably distorted and compressed (fig 6) The various nerve cells, including the vegetative nerve cells, showed all types of pathologic change The nerve cells of the hypothalamic region appeared normal

CASE 8—*Metastatic carcinoma to the cerebellar vermis with compression of the metencephalon Ocular manifestations Pathologic evidence of increased intracranial pressure*

F E, a man aged 59, with carcinoma of the lung, had sudden onset of hyperthermia, headache, dizziness, nausea, vomiting, cerebellar signs and episodes of lethargy, from which he could be aroused

Neurologic Examination—Examination revealed papilledema, dilated pupils, which reacted sluggishly to light, lateral deviation of both eyes, cerebellar signs, involving especially the trunk and head, residual paralysis of the left facial nerve of peripheral type, dysphonia and slight dysphagia, and depressed reflexes in the lower extremities, with a positive Babinski sign on the right

Course—Later, there appeared pronounced rigidity, bilateral forced grasping, episodes of stupor, from which he could still be aroused, and disorientation

Laboratory Data—The urea nitrogen of the blood was 17 5 mg per hundred cubic centimeters The spinal fluid showed a slight increase in protein and a pressure of 100 mm of water

Autopsy—There was uniform dilatation of the entire ventricular system Metastatic nodules were present in the vermis cerebelli in the region of the lobulus biventer bilaterally (fig 7) and in the meninges of the brain stem The brain stem was compressed The fourth ventricle was obliterated (fig 7) Some of the nerve cells of the vagus nerve and those of the vegetative nervous system appeared shadow-like and showed

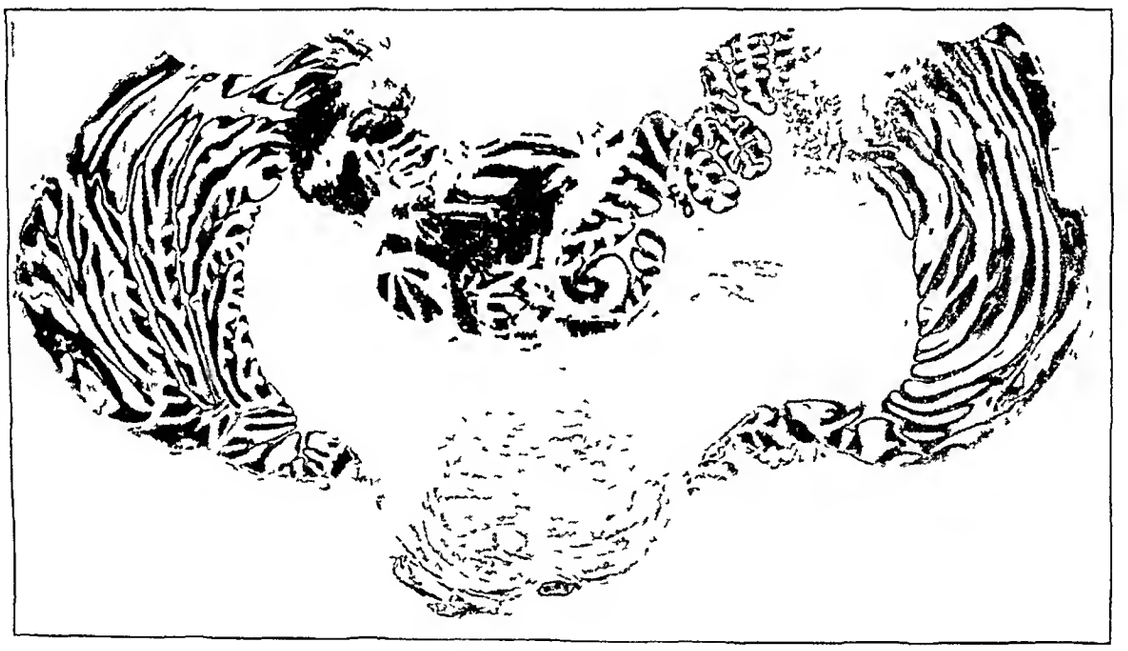

Fig 7 (case 8)—Metastatic carcinoma to the cerebellar vermis

chromatolysis and slight disintegration The hypothalamus was normal

Comment.—The episodes of the lethargy and hyperthermia in this case were undoubtedly caused by the tumor of the posterior fossa obliterating the fourth ventricle and compressing the medulla oblongata

LESIONS AT MESENCEPHALOMETENCEPHALIC LEVEL

There is some evidence, especially clinical, that somnolence or other disturbances in sleep mechanism may result from lesions at the mesencephalometencephalic level Righetti [1] (1903), in analyzing 115 cases of gliomas of the posterior fossa with pathologic sleep, found tumors in the region of the medulla oblongata in 28 per cent, tumors of the corpora quadrigemina and epiphysis in 26 per cent and tumors of the cerebellum in 16 per cent Babonneix and Widiez [2] reported a case of somnolence associated with a glioma of the quadrigeminal bodies Mikheev [3] found lesions in the region of the thalamus and the periaqueduct gray matter in 5 cases Mauthner,[4] in 1890, and von Economo,[5] in 1916, induced somnolence by producing experimental lesions in the periventricular gray substance of the third ventricle and neighboring portions of the aqueduct Marinesco and others [6] concluded that the region around the aqueduct was more directly concerned with the function of sleep than the most anterior portion of the periventricular gray matter Potzl [7] placed the center for sleep disturbances in the region of the nuclei of the posterior longitudinal bundles Retif [8] stated the belief that there is a reciprocal inhibition between the mesencephalic center and the cerebral cortex Lucksch [9] expressed the opinion that both the hypothalamus and the neighboring portions of the mesencephalon and thalamus are concerned with sleep but are subject to the control of the cerebral cortex Hechst [10] stated the belief that the brain stem, the medial part of the posterior third of the thalamus and the contiguous region, comprising the posterior third of the periventricular gray matter and the anterior part of the periaqueductal gray substance, play an equal role in disturbances of sleep

Many investigators have indicated the relation of lethargy in encephalitis to ophthalmic signs and have attributed the somnolence to involvement of the nuclei of the ocular nerves, which are situated in the mesencephalon and metencephalon Frank,[11] on the basis of his study on the oculomotor nuclei of mammals, suggested that the pars lateralis of the nucleus subfascicularis belongs to the sleep-regulating center and that in it is localized the most important component of sleep, paresis of the eyelids Another sleep component, hypotonus, according to him, is localized in the pars dorsalis of the nucleus intraconjunctivalis centralis Others (von Stockert,[12] Kahn [13]) also asserted that there is a connection between sleep and the ocular mechanisms Although in all our cases of the mesencephalometencephalic group and in some of the hypothalamic group interference in function of the ocular mechanism was disclosed, the absence of such dysfunction in the other groups and the lack of sleep disturbances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism

On the basis of the experimental and anatomicopathologic observations in some cases, it may be stated that lesions at the junction of the mesencephalon and the diencephalon result in disturbance of the sleep mechanism, especially hypersomnia It should be remembered that the descending hypothalamic pathways are situated in the mesencephalon and metencephalon Injury of these structures at this level may result in the same disturbances as injury at their point of origin, that is, in the hypothalamic area

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The two known pathways connecting the hypothalamus and the brain stem are (1) the mamillary peduncle, an afferent pathway of mesencephalic origin, ending chiefly in the lateral mamillary nucleus, and (2) the mamillotegmental tract, an efferent pathway, most likely arising from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain An efferent connection demonstrated only physiologically is the vagosupraoptic system

In our groups, there were 8 cases in which neoplasm occurred at the mesencephalometencephalic level (table) In 4 cases the tumors

Summary of Observations in 8 Cases of Disturbances of Sleep Associated with Mesencephalic and Metencephalic Lesions

	Cases
Hemangioblastoma of cerebellum	3
Metastatic carcinoma to cerebellar vermis	1
Glioblastoma multiforme of mesencephalon	1
Medulloblastoma of metencephalon	1
Meningioma of cerebellopontile angle	1
Spongioblastoma polare of mesencephalon	1
Compression or invasion of brain stem	8
Involvement of hypothalamus	0
Evidences of increased intracranial pressure (in 1, no clinical evidence, but internal hydrocephalus)	8
Ocular manifestations (in 2, only evidence of nystagmus)	8
Endocrine disturbances (in 1, loss of libido without changes in the genitals)	0
Deviation from normal temperature	
Slight hypothermia	2
Hyperthermia	1
Inversion of sleep mechanism	1

were situated in the cerebellum and the fourth ventricle, in 3 of these cases the tumor was a hemangioblastoma and in 1 a metastatic carcinoma (cases 1, 2, 3 and 8) In the other 4 cases the tumors were, respectively, spongioblastoma polare of the mesencephalon (case 5), glioblastoma multiforme of the mesencephalon (case 6), medulloblastoma of the metencephalon (case 4) and meningeal fibroblastoma in the cerebellopontile angle (case 7) Compression or invasion of the brain stem was present in all cases In none was there direct or indirect involvement of the hypothalamus — its nerve cells were normal Evidence of increased intracranial pressure was present in all cases, in 1 case no clinical evidences but internal hydrocephalus was noted at autopsy A high incidence of increased intracranial pressure in this group should be expected, as in all cases the neoplasm encroached on the fourth ventricle or the aqueduct of Sylvius Ocular manifestations, consisting of diplopia, paresis of ocular muscles and nystagmus, were present in all cases, in 2 cases only nystagmus was shown Endocrine disturbances were absent, 1 patient had loss of libido without any changes in the genitalia Slight hypothermia was present in 2 cases and hyperthermia in 1 case Inversion in the sleep mechanism was noted in 1 case In practically all these cases the descending hypothalamic pathways and the nerve cells of the vegetative system of the brain stem were involved

SUMMARY AND CONCLUSION

In 8 cases of pathologic sleep there was involvement of the mesencephalon and metencephalon The hypothalamus was normal in all cases In all the cases there was implication of the descending hypothalamic pathways and the nerve cells of the vegetative nervous system of the brain stem

Increased intracranial pressure was present in all cases The high incidence of increased intracranial pressure in this group should be expected, as in all cases the neoplasm encroached on the fourth ventricle or the aqueduct of Sylvius

Ocular manifestations, consisting of diplopia, paresis of ocular muscles and nystagmus, were present in all instances, in 2 cases only nystagmus was shown This phenomenon should be expected because of the location of the nuclei of the oculomotor nerves in this part of the central nervous system The lack of sleep disturbances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism

Slight hypothermia was present in 2 cases and hyperthermia in 1 case

From this series of cases, it can be assumed that lesions of the ascending and descending hypothalamic pathways of the mesencephalon (mamillary peduncle and mamillotegmental tract) and some of the vegetative nervous centers in the brain stem result in disturbances of the sleep mechanism

Montefiore Hospital for Chronic Diseases

STUDIES IN DISEASES OF MUSCLE

XV PROGRESSIVE SPINAL MUSCULAR ATROPHY AS A LATE SEQUEL OF ACUTE EPIDEMIC ENCEPHALITIS, REPORT ON TWO CASES

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Progressive spinal muscular atrophy as a late sequel of acute epidemic encephalitis has been described by several authors, but the possibility of its occurrence is not generally acknowledged The entity is of interest, not only for a more complete understanding of epidemic encephalitis but for its possible etiologic relationship to certain instances of amyotrophic lateral sclerosis and chronic progressive anterior poliomyelitis It is for the latter reason that the following 2 cases are reported

REPORT OF CASES

CASE 1.—*History*.—The patient, a Polish-born salesman, aged 50, was first seen in the New York Hospital on May 14, 1940, complaining of immobility of the face, progressive weakness of the left arm and increasing tremor of both upper extremities About nine months previously, he first noted tremor, weakness and fatigability of the left upper extremity At about the same time there developed a severe cramp in the fingers of the left hand, during which the fist was tightly clenched and could not be opened voluntarily Similar attacks of cramp occurred on two subsequent occasions About one month after the onset of muscular weakness, the patient's relatives observed that the face lacked its former mobility and expression, that the eyes blinked infrequently and that the mouth hung open All symptoms progressed steadily, and five months after their onset the patient noted tremor of the right arm and the chin

The past personal history was significant in that the patient had an acute febrile illness in 1921 For a period of seventeen days he had fever and a sharp, steady pain which radiated from the left shoulder to the hand During the entire course of the acute illness the patient was unable to sleep, a difficulty which he attributed not to the pain but to loss of ability to fall asleep He was seen by several neurologists, each of whom diagnosed the condition as acute epidemic encephalitis After the subsidence of the acute symptoms the patient had generalized muscular weakness, which gradually improved but which made it necessary for him to be absent from his work for eight months Thereafter, the patient was entirely free from symptoms until the onset of his present illness, about seventeen years later

In 1914 he underwent an operation for enucleation of the left eye following injury by a fragment of steel

Examination.—The patient was a well developed and obese man He walked with the left arm extended and held close to the body The facies was masklike, the eyes blinked infrequently, and the mouth hung open The voice was of monotonous quality There were moderate fibrillations and slight atrophy of the tongue The infraspinatus and deltoid muscles on the left side showed considerable wasting, but the remaining muscles of the left upper extremity, including the small muscles of the hand, were reduced only slightly in volume All these muscles showed reduction in power that was proportional to the amounts of wasting There were slight wasting and weakness of the right deltoid muscle A moderate number of muscular fasciculations were seen over the front of both shoulders and the upper part of the thorax There was moderate tremor of the fingers of the left hand when the extremity was at rest, when the hand was engaged in purposeful movement, the tremor disappeared Both upper extremities showed slight rigidity of cogwheel type on passive movement The tendon reflexes were reduced but equal on the two sides The remainder of the neurologic examination revealed essentially a normal condition

Course of Illness from May 14 1940 to Oct 18, 1942.—The patient was seen at frequent intervals in the outpatient department Under a regimen of 0 3 mg of scopolamine hydrobromide four times daily, there was moderate decrease in muscular tremor and rigidity for about four months, after which time these symptoms increased slowly but steadily Each time the medication was discontinued or the dosage decreased, the symptoms increased Progression in muscular disability was steady during the entire period of observation In January 1941, weakness of the right hand was noted, in March 1941, the patient was barely able to lift the left arm from the side of the body, and in December of the same year, the right shoulder was affected to the extent that the hand could be lifted only as high as the shoulder when the elbow was extended At about the same time, he began to complain of frequent cramps in the calves and feet at night Occasionally a "cramp" in the tongue interfered with talking In February 1942, all the muscles of the shoulder girdle showed considerable wasting, and for the first time definite wasting of the forearms and hands was noted Fasciculations were absent The right upper extremity showed definite rigidity of cogwheel type on passive movement, but the left upper extremity, which now hung limp against the side of the body, no longer showed increased resistance to passive stretch In May 1942, the patient began to complain of edema of the left hand in the evenings This was relieved to a moderate degree when the hand and forearm were supported by a sling above the level of the waist In May 1942, Dr J Casals,

From the Departments of Psychiatry and Medicine, Cornell University Medical College and the New York Hospital

of the Rockefeller Institute for Medical Research, tested a sample of the patient's blood for complement-fixing antibodies against antigens of eastern and western equine encephalomyelitis, St Louis encephalitis and lymphocytic choriomeningitis The reactions to all tests were negative In September 1942, the patient began to have considerable dyspnea and orthopnea and found it necessary to use two pillows at night On Oct 18, 1942, he was admitted to the New York Hospital for further investigation

Second Examination—The following neurologic signs were present masklike immobility of the facies, coarse

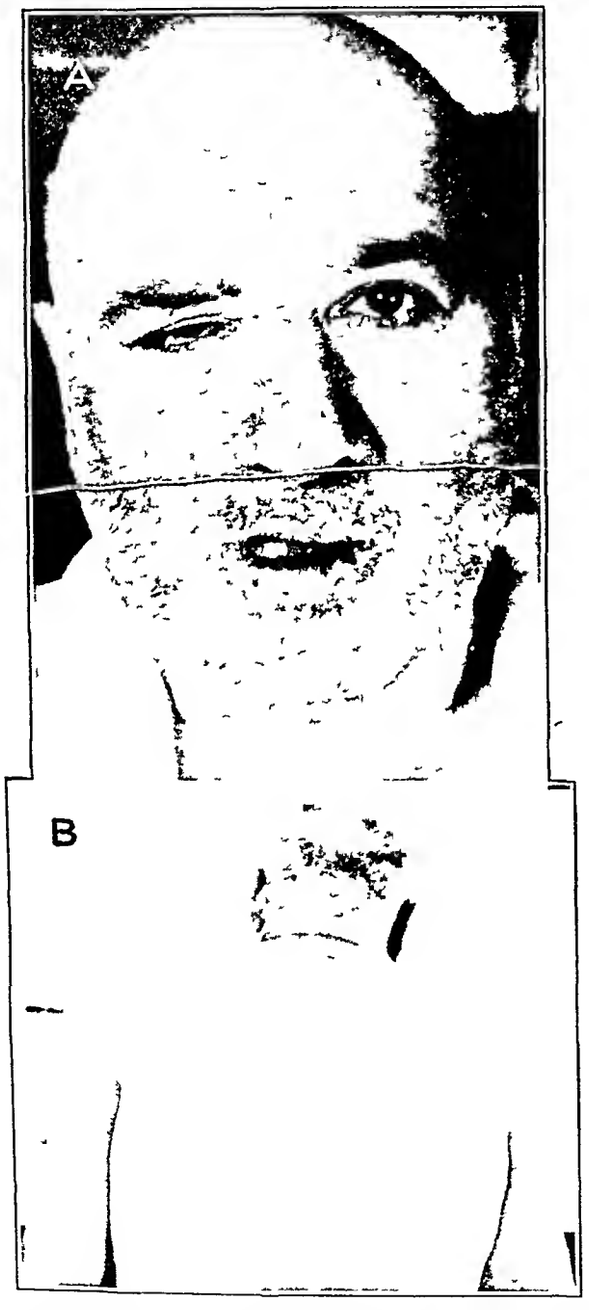

Fig 1 (case 1)—*A*, drooping jaw, partial protrusion of tongue and immobile facies characteristic of paralysis agitans *B*, wasting of muscles of the shoulders and upper portion of the arms

tremor of the jaw, moderate atrophy, fibrillary twitchings and coarse tremor of the tongue, difficulty in phonation, monotonous speech, considerable wasting of the muscles of the shoulder girdle and of both upper arms, which was more advanced on the left side, moderate atrophy of the muscles of the forearms and hands fasciculations of the muscles of both shoulders and upper extremities, gross spasms of the muscles of both calves, and fasciculations of the muscles of both thighs The patient was practically unable to make any voluntary movement with the left upper extremity and could raise the right arm only as high as the level of the shoulder Resistance to passive stretch was diminished in both upper extremities Muscular power was slightly reduced in the lower extremities, where resistance to passive stretch was slightly increased The tendon reflexes in the upper extremities were absent except for the biceps reflex, which could barely be elicited The deep reflexes in the lower extremities were exaggerated, but ankle clonus was absent and the plantar response was of flexor type bilaterally The superficial abdominal and cremasteric reflexes were active and equal on the two sides There were no sensory defects

In addition, the blood pressure was elevated, the systolic pressure was 154 and the diastolic 112 mm of mercury The heart was moderately enlarged, but there were no murmurs

Examination of the blood showed 5,300,000 red cells per cubic millimeter, 18 9 Gm of hemoglobin per hundred cubic centimeters and 10,800 white cells per cubic millimeter, with a normal differential count The Kline reaction of the blood was negative The concentrations of calcium, phosphorus, potassium, sodium and uric acid in the serum were 10 1, 3 8, 16, 335 and 3 2 mg per hundred cubic centimeters, respectively The phosphatase activity of the blood was 2 8 Bodansky units

The spinal fluid was under normal pressure and contained no cells The concentrations of sugar, chlorides and protein in the spinal fluid were 61, 580 and 30 mg per hundred cubic centimeters, respectively The Wassermann reaction was negative, and the colloidal gold curve was normal

Two dextrose tolerance tests gave essentially normal results except that the level of the blood sugar determined three and a half hours after ingestion of the dextrose was low (45 and 55 mg per hundred cubic centimeters) The circulation time of the blood was nineteen seconds Venous pressure in the right arm was 9 cm of water The basal metabolic rate was + 14 per cent

Roentgenograms of the skull and of bones of the extremities revealed no pathologic changes Fluoroscopic examination of the thorax showed that the diaphragm was high on both sides, extending to the level of the third anterior intercostal space on the right side and to the fourth intercostal space on the left side No movement of the diaphragm was seen on repeated respiration

About one week after his admission the muscular cramps gradually disappeared The patient was discharged from the hospital on Nov 2, 1942

Subsequent Course—During the next seven months the patient was seen on several occasions, when steady progression in muscular wasting was noted In February 1943, he again began to complain of cramps in the calves, and the right hand was found to be much weaker In May of the same year, the patient had increasing difficulty in respiration In June, weakness of all four extremities was increased, muscular cramps, which occurred nightly, were severe, and speech was indistinct The following month the patient died of paralysis of the respiratory muscles

Case 2—The patient, a male bank clerk, aged 34, was first seen in the New York Hospital on Sept 19,

1943, with the complaint of weakness and wasting of the arms and legs

In 1924 he had a severe febrile illness, which was diagnosed as acute epidemic encephalitis After a period of two weeks, during which he was delirious, the illness gradually subsided, and the patient appeared to have recovered completely He had good health until nine years later, when he began to complain of increasing weakness of the right arm, which was followed in a few months by similar disability in the left arm At about the same time he noted frequent "twitchings" in the muscles about the shoulders and observed gradual diminution in volume of the upper portion of the arms The weakness and wasting progressed slowly but steadily and extended to all the muscles of the upper extremities Eight years after the onset of muscular weakness in the arms, the patient began to fall often, owing to sudden "buckling up" of the knees A few months later, increasing difficulty in walking, in climbing stairs and in getting up from a sitting position was noted Fasciculations, similar to those in the upper extremities, were seen in the thighs

The past personal and family histories were noncontributory

Examination.—The patient swayed from side to side while walking, the trunk slumped forward, and the arms hung limply at the sides of the body He was unable to sit up from a lying-down position without using his arms as supports The pupils, the extraocular movements and the fundi were normal There was no facial weakness The tongue was without atrophy or adventitious movements The muscles of the neck were of good power Both scapulas showed definite winging There was advanced wasting of all the muscles of the upper extremities, with diminution in power which was proportional to the wasting The hands were of main en griffe type The biceps and triceps reflexes could not be elicited No adventitious movements were seen in the muscles of the upper extremities The superficial abdominal reflexes were absent There were moderate wasting and weakness of the muscles of the thighs, but the muscles of the calves and feet were of normal volume and power Occasional fasciculations were seen in the thighs, but all muscles below the knees were without adventitious movements The patellar and achilles reflexes were sluggish but equal on the two sides There was no ankle clonus The plantar reflex was of flexor type bilaterally There was no increase in resistance to passive stretch in any of the extremities Sensibility for pain, light touch, temperature, vibration and position was normal There were no signs suggestive of paralysis agitans

COMMENT

Both patients had a severe attack of acute epidemic encephalitis, from which they appeared to recover completely One of them had severe pain in an upper extremity, but neither showed evidence of involvement of motor nerves during the acute illness Several years after the attack of acute encephalitis, both patients presented muscular fasciculations and progressive wasting, which began in the muscles about the shoulders but later affected other groups One patient had paralysis agitans, which had its onset at about the same time as the muscular atrophy

One patient is still alive, ten years after onset of muscular symptoms, in the other signs of bulbar involvement developed, and he died four years after muscular wasting first was noted

Muscular paralysis is not unusual during the acute stage of epidemic encephalitis However, progressive muscular wasting of the types commonly seen with progressive anterior poliomyelitis and amyotrophic lateral sclerosis is relatively rare

Progressive spinal muscular atrophy has been observed to occur in the following three circumstances (1) during a chronic phase of epidemic encephalitis, (2) shortly after the initial acute attack of epidemic encephalitis has subsided, and (3) after a long interval, of several months or years, following apparent complete recovery from the acute infection

Froment and Gennevois [1] reported a case of unilateral muscular atrophy of Aran-Duchenne type in a woman who had had an attack of "grip" six months before the onset of muscular symptoms In the case of Gutmann and Kudelski [2] there developed muscular wasting resembling dystrophy of fascioscapulohumeral type one and a half months after a severe attack of epidemic encephalitis, which was associated with an intense "crawling" sensation in the cervical and scapular areas Froment [3] reported the case of a woman aged 24 who had encephalitis, with continuous low grade fever for several months, during which period there were progressive muscular wasting, exaggerated reflexes, fasciculations and myoclonus Bulbar signs developed, and the patient died within three years from onset of the illness The anatomic lesions were characteristic of amyotrophic lateral sclerosis Sicard and Paraf [4] stated that they had seen 6 cases of muscular atrophy with fasciculations associated with chronic epidemic encephalitis, however, in all instances the wasting was localized to a few muscular groups and improved steadily The authors expressed the opinion that in epidemic encephalitis the process can extend to the spinal cord, spinal roots and

1 Froment, J, and Gennevois, E Atrophie musculaire progressive myelopathique et encephalomyélite myoclonique, Rev neurol **28** 726, 1921

2 Gutmann, R A, and Kudelski Encephalite lethargique datant de cinq ans avec sequelles myopathiques a type Landouzy-Dejerine, Bull et mem Soc med d hop de Paris **45** 24, 1921

3 Froment, J Sclerose laterale amyotrophique et encephalite epidemique, Rev neurol **32** 842, 1925

4 Sicard, J A, and Paraf, J Encephalites amyotrophiques, de type radiculaire ou peripherique, Bull et mem Soc med d hop de Paris **44** 1289, 1920

peripheral nerves Netter [5] postulated that the virus of epidemic encephalitis can affect various parts of the central and peripheral nervous system The patient of Guillain and Alajouanine [6] had muscular atrophy of the upper extremities, exaggerated tendon reflexes, bulbar signs and many features of paralysis agitans Three years before the onset of muscular symptoms the patient had had a severe attack of encephalitis, with insomnia for two months and severe pains in the upper portion of the arms and the scapular areas Euzière, Pagès and Janbon [7] reported a case of progressive muscular atrophy of six years' duration, which had its onset immediately after an acute attack of epidemic encephalitis The authors designated the condition as "chronic epidemic encephalitis in a form of anterior poliomyelitis" Carr [8] observed a man aged 29 who had encephalitis with diplopia, followed by somnolence, intermittent diplopia and soreness of the muscles for three years Examination seven years after the acute infection showed wasting and fasciculations of the muscles of the shoulder girdle Wimmer [9] reported 5 cases of amyotrophic lateral sclerosis subsequent to chronic epidemic encephalitis In 2 of these cases muscular wasting followed almost immediately the initial stage of the infection In two later reports, Wimmer [10] gave a summary of 20 cases of spinal muscular atrophy in patients with a previous history of encephalitis In 2 of these cases the muscular wasting was most pronounced in the proximal groups Of the entire series of 20 patients, 4 had paralysis agitans Jancsó,[11] Nyssen and van Bogaert [12] and Ornsteen [13] reported instances of amyotrophic lateral sclerosis following epidemic encephalitis The patient of Illing [14] noted muscular stiffness and drooling of saliva four years after an attack of acute encephalitis Seven years after the acute infection there were stiffness of various muscle groups and wasting of the hands The condition progressed steadily, and three years later the hands were of the main en griffe type The muscles of the shoulder and pelvic girdle were without wasting The author expressed the opinion that this was an instance of epidemic encephalitis with subsequent paralysis agitans and extension of the process to the spinal cord Yealland's [15] patient had slowly progressive weakness of ten years' duration and tremor of Parkinson's type for four years There was no history of an acute infection The patient of Lhermitte, Thibault and Ajuriaguerra [16] gave a history of paralysis agitans immediately following a typical attack of acute encephalitis Seven years later amyotrophic lateral sclerosis developed The course was progressive until his death, thirteen years after the acute attack of encephalitis Although the clinical picture resembled that of typical amyotrophic lateral sclerosis, as described by Charcot, there were notable histologic differences The degenerative changes in the spinal cord were not as uniform in their intensity as are found in typical cases The tracts of Flechsig and Gower were more affected than were the crossed pyramidal tracts, and the posterior tracts were intact The cells of the anterior horns were reduced in number and size Decourt, Mathieu and Meyer [17] and Khait [18] reported on patients

5 Netter, in discussion on Sicard and Paraf [4]

6 Guillain, G, and Alajouanine, T Sclerose laterale amyotrophique avec contracture intense du type extrapyramidal (hypertonic plastique et exageration des reflexes de posture) Discussion de son etiologie encephalitique, Rev neurol **33** 337, 1926

7 Euziere, J, Pages, P, and Janbon, M Poliomyelite anterieure chronique consecutive a une nevraxite epidemique, Bull Soc sc med biol Montpellier **7** 85, 1926, abstracted, Zentralbl f d ges Neurol u Psychiat **44**·80, 1926

8 Carr, A D An Encephalitic Residual Simulating Progressive Muscular Atrophy of Shoulder Girdle Type, Arch Neurol & Psychiat **16** 344 (Sept) 1926

9 Wimmer Amyotrophies de type sclerose laterale amyotrophique dans l'encephalite epidemique chronique, Rev neurol **32** 841, 1925

10 Wimmer, A, and Neel, A V Les amyotrophies systematisees dans l'encephalite epidemique chronique, Acta psychiat et neurol **3** 319, 1928 Wimmer, A Les amyotrophies systematisees dans l'encephalite epidemique chronique, Acta med Scandinav, 1928, supp 26, p 392

11 Jancso, S Ueber ein nach Encephalitis epidemica beobachtetes, der amyotrophischen Lateralsklerose ahnliches Krankheitsbild, Klin Wchnschr **7** 2442, 1928

12 Nyssen, and van Bogaert, L Forme médullaire de l'encéphalite epidémique chronique, J d neurol et psychiat **28**.114, 1928

13 Ornsteen, A M The Syndrome of Amyotrophic Lateral Sclerosis in Epidemic Encephalitis, J Nerv & Ment Dis **82** 369, 1930

14 Illing, E Uebergreifen der Encephalitis lethargica auf das Ruckenmark, Monatschr f Psychiat u Neurol **82**·177, 1932

15 Yealland, L R Progressive Muscular Atrophy Associated with Paralysis Agitans, Proc Roy Soc Med **31** 211, 1938

16 Lhermitte, L, Thibault, and Ajuriaguerra Syndrome de sclérose latérale amyotrophique d'origine encephalitique, Rev neurol **45**.372, 1938

17 Decourt, J, Mathieu, P, and Meyer, L Syndrome de sclerose laterale amyotrophique consecutif à une encephalite lethargique, signes extrapyramidaux associes, Rev neurol (pt 2) **41** 596, 1934

18 Khait, M B Syndrome of Amyotrophic Lateral Sclerosis Developing After Epidemic Encephalitis, Sovet psikhonevrol (nos 4-5) **15**.85, 1939, abstracted, Zentralbl f d ges Neurol u Psychiat **97** 400, 1940

with amyotrophic lateral sclerosis following epidemic encephalitis. Both patients showed evidence of involvement of the extrapyramidal system.

More recently, Wechsler, Sapirstein and Stein[19] reported 2 cases of amyotrophic lateral sclerosis immediately following acute infection of the nervous system.

Numerous authors, including Matzdorff[20] and Poussepp and Rives,[21] have expressed the opinion that in some cases of amyotrophic lateral sclerosis there is evidence that the process is of infectious origin. While there appears to be little doubt that the spinal cord can be involved early in an attack of epidemic encephalitis (Kraus,[22] Calhoun,[23] Grinker[24] Mingazzini[25] Gross,[26] Stern[27] and Cruchet and Verger[28]), evidence for the occurrence of amyotrophic lateral sclerosis as a sequela several years after the acute infection is less convincing. However, the cases which are reviewed in this report and the data in my first case indicate the strong probability of such an occurrence. It appears that involvement of various parts of the nervous system in acute epidemic encephalitis may not be as unusual as is commonly assumed. As a matter of fact, in their studies on "spring-summer encephalitis" in Russia, Robinzon and Sergeeva[29] regularly found diffuse involvement of the entire nervous system, especially of the anterior horn cells of the upper spinal segments. Whether this early involvement of the anterior horn cells and other structures of the spinal cord during the acute infection is related to subsequent degenerative changes of amyotrophic lateral sclerosis or chronic anterior poliomyelitis can only be speculated on at present.

SUMMARY

Two cases of progressive muscular atrophy with onset several years after an attack of acute epidemic encephalitis are reported. In 1 instance the clinical picture was that of chronic anterior poliomyelitis, in the other the changes were those of amyotrophic lateral sclerosis and paralysis agitans.

525 East Sixty-Eighth Street (21)

19 Wechsler, I. S., Sapirstein, M. R., and Stein, A.: Primary and Symptomatic Amyotrophic Lateral Sclerosis: A Clinical Study of Eighty-One Cases, Am. J. M. Sc. **208**: 70, 1944.

20 Matzdorff, P.: Zur Pathogenese der amyotrophischen Lateralsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**: 703, 1925.

21 Poussepp and Rives: Contribution a la pathologie et a la pathogenie de la sclérose latérale amyotrophique, Rev. neurol. **32**: 834, 1925.

22 Kraus, W. M.: An Unusual Case of Epidemic Encephalomyelitis, J. Nerv. & Ment. Dis. **52**: 142, 1920.

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27 Stern, F.: Encephalitis Epidemica, Fortschr. d. Neurol., Psychiat. **1**: 205, 1929, cited by Illing[14].

28 Cruchet, R., and Verger, H.: Les formes basses de l'encephalomyelite epidemique, myelites, radiculites, polynevrites, Presse méd. **34**: 737, 1926.

29 Robinzon, I. A., and Sergeeva, J. I.: Pathologo-Anatomical Changes in the Nervous System Associated with Spring-Summer (Forest) Encephalitis, Arch. biol. nauk. **56**: 71, 1939, abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **97**: 9, 1940.

News and Comment

SECOND SOUTH AMERICAN CONGRESS ON NEUROSURGERY

The second South American Congress on Neurosurgery will be held in Santiago, Chile, in April 1947

The following subjects have been assigned to the various neurosurgical groups in Argentina, Brazil, Chile, Peru and Uruguay

1 Hydrocephalus (*a*) Classification, Peru, (*b*) Pathology, Argentina, (*c*) Clinical aspects, Brazil, (*d*) Treatment, Argentina

2 Histology of Brain Tumors in Relation to Clinical Symptoms (*a*) Pathology and clinical course, Argentina, (*b*) Pathology and surgical treatment, Argentina, (*c*) Pathology and radiotherapy, Uruguay

3 Brain Abscess (*a*) Pathology, Uruguay, (*b*) Clinical aspects of cerebral abscess, Brazil, (*c*) Clinical aspects of cerebellar abscess, Argentina, (*d*) Treatment, Chile

The program will also provide time for open discussions, practical demonstrations and moving picture projections.

Inquiries may be directed to Dr Alfonso Asenjo, Director, Central Institute of Neurosurgery, Santiago, Chile

REFRESHER COURSE IN PSYCHIATRY AND NEUROLOGY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE

Beginning Sept 17, 1946, an eight weeks' full time refresher course in psychiatry and neurology will be given for physicians at the New York University College of Medicine, Psychiatric Pavilion, Bellevue Hospital, New York Instruction will be given by the staffs of the psychiatric and neurologic departments of the medical college, with the assistance of staff members from other divisions of the medical school The subjects covered will include clinical psychiatry, clinical neurology, functional and organic psychoses, psychoneuroses, psychopathology, therapy, psychosomatic problems, neuroanatomy, neurophysiology, neuropathology, roentgenologic diagnosis, electroencephalography and other related subjects

Registration is open to graduates of approved grade A medical schools who have completed an approved internship in medicine Preference will be given to applicants who have had previous approved psychiatric training and to those who are preparing for examination by the American Board of Psychiatry and Neurology

Early application on an approved form for registration is recommended because of the limited enrolment which can be accommodated The tuition fee is $250

Additional information may be obtained from Dr S Bernard Wortis, professor of psychiatry New York University College of Medicine, 477 First Avenue, New York City 16

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

A new publication, the *Quarterly Review of Psychiatry and Neurology*, under the editorship of Dr Winfred Overholser, professor of psychiatry, George Washington University School of Medicine, and superintendent of St Elizabeths Hospital, is being launched by the Washington Institute of Medicine Like the quarterly reviews in other fields of medicine published by the Washington Institute, this publication will consist of abstracts of articles of psychiatric and neurologic interest from journals from all parts of the world The annual subscription is $9

OFFICIAL METHOD OF RECORDING PSYCHIATRIC DIAGNOSES AND REVISED NOMENCLATURE ADOPTED BY UNITED STATES ARMY

The Army has adopted for its official use a new method of recording a psychiatric diagnosis and a revised nomenclature, as set forth in War Department Technical Medical Bulletin, No 203, dated Oct 19, 1945 This was adopted after an extensive study during 1944 and 1945, during which time suggestions were obtained from a large number of leading civilian and military psychiatrists

This Bulletin will prove valuable as a means of standardizing terminology in hospital, clinic and private practice In many ways it resembles the "Standard Nomenclature of Disease" but, in addition, presents criteria of diagnosis in psychiatric conditions It may be obtained from the Superintendent of Documents, Washington, D C

PROJECT IN INTERNAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE

Cornell University Medical College announces a project in internal medicine at the New York Hospital, designed to deal clinically and experimentally with psychosomatic patients There are three main objectives (1) to develop a practical method of dealing with ambulatory clinic patients who suffer from symptoms related to their emotional states and life situations, (2) to engage in experimental study of the mechanisms involved in illness of this nature and (3) to train especially able young physicians in experimental methods and a critical psychosomatic approach to the care of the sick Approximately half of the time will be spent in the diagnosis and management of patients and half of the time in research dealing mainly with mechanisms underlying symptoms

The project will be directed by Dr Harold G Wolff with the assistance of an internist, Dr Stewart Wolf, a psychiatrist, Dr Herbert S Ripley Jr, and six fellows Fellows will be appointed for a period of one year, with the expectation of serving for two years or more Their salary for the first year will be $2,500 Candidates for fellowships should have at least two years' training in internal medicine and have given evidence of a psychiatric orientation They need not have had experience in research but must have a serious interest in investigation, energy and curiosity

Prospective candidates should arrange for a personal interview through Dr David P Barr, professor of medicine, the New York Hospital, 525 East 68th Street, New York

Obituaries

PETER BASSOE, M D
1874-1945

Peter Bassoe was born May 18, 1874, at Drammen, Norway, the son and grandson of Lutheran ministers His father was beloved by his congregation but was impractical and improvident, his mother was rather dogmatic and apt to make a scene when opposed, these facts are of importance in evaluating his subsequent career After completing the Cathederal School in Oslo, he came to America, at the age of 19 years He had a relative in Chicago, but when he arrived here, in the midst of a depression, in 1893, he found this relative out of work and more in need of assistance than himself So he moved on to the home of his father's cousin, the Rev Dr Laur Larsen, president of Luther College, Decorah, Iowa There he began teaching country school, boarding around in the manner of those times The following year he entered the old College of Physicians and Surgeons in Chicago, assisting in chemistry and working at any odd jobs he could find to pay for his schooling When he graduated, in 1897, he took the competitive examination for interns at the Cook County Hospital and made first place The following year found him assistant physician in the state hospital at Mount Pleasant, Iowa, and two years later he went to the state hospital in Worcester, Mass., where he worked with Adolf Meyer In 1901 he made a trip to Europe After a brief stay in Heidelberg and Montpellier, he moved on to Prague, where he fell seriously ill with nephritis He returned to Chicago in 1902 and occupied a position as pathologist at the Presbyterian Hospital, with which institution he was to remain associated until his death In 1906 he again went to Europe, this time to Berlin, Paris and London, where he visited the neurologic clinics On returning to this country, in 1907, he became attending neurologist to Cook County Hospital and assistant to Dr Hugh T Patrick He was also placed on the staff of the Presbyterian Hospital, as assistant attending neurologist, and on the faculty of Rush Medical College, as assistant professor of nervous diseases Thus, he was definitely launched on his career, his formal student days were over but he never ceased to study, his thirst for knowledge ended only with his last breath The struggle to obtain an education was hard, and he could expect only moral support from Dr Larsen, who had a large family to support on a meager salary He was wont to relate interesting experiences with free lunch counters during this period

In 1907, also, he married Miriam Gardner, who had just graduated from Rush Medical College I doubt that she could have been more useful to society as a practitioner of medicine than as Mrs Bassoe At least her husband had no qualms of conscience at ruining a good physician He remarked often on his good fortune in finding the perfect helpmeet, one, moreover, so gracious, equable and amiable as to make his home a haven of rest and recuperation from the worries and strains of his professional life He was grateful for his contrast with his home life during his boyhood, as, indeed, he was grateful for all the blessings which came his way As his family grew in numbers, he moved to Evanston, where his friends knew him in the big, rambling house on Michigan Avenue, which always seemed to be the perfect setting for him His main relaxation was caring for its grounds and garden He had little interest in the fine arts, and it was difficult to get him out for anything except a medical meeting or a serious lecture on some instructive subject He also did not care much for games, although some one taught him to pitch horseshoes, and many a pleasant game we had until his weakened heart made even this mild exertion inadvisable

As is too often the case with suburbanites, he had not much time for local civic affairs, leaving such matters to his wife, who was for many years a member of the school board, the town was too far from the office and hospitals where his practice was carried on The long journey to and from his work left him little time, and this he spent in writing and in reading and abstracting the current literature of neurology and psychiatry In 1910 he became associated with Dr Patrick in editing the "Year Book of Neurology," and in 1918 he took over the sole editorship, which he held until an illness in 1933 caused him to relinquish it In this role he initiated the policy of writing pithy prefaces to

Read at a meeting of the Illinois Psychiatric Society, Chicago, Dec 6, 1945

the yearly summaries, a practice which his successor, Dr Hans Reese, has continued and amplified In this work he was greatly aided by his wife and, later, by his daughters, who still remember then pride as they became old enough, one by one, to help their father in this way It was in this occupation that his thorough knowledge of neurology was built up and maintained He was constantly alert to all the latest developments in his field, an example of it was his prompt recognition of epidemic encephalitis in 1918

Dr Bassoe had an erudite mind He was a pioneer in neuropathology in the Middle West, and most of his writings are of a clinicopathologic nature, for which his experience as pathologist so well fitted him He took little part in the development of histopathology except as collaborator with others, notably Hassin and Grinker, being handicapped by the demands of a busy practice and by working in an institution in which the neurologist was a mere adjunct to the medical clinic It is true that there was a neuropathologic laboratory, but its equipment was antediluvian, and it was dominated by a physician who seemed interested mainly in conducting a graveyard for brains By the time Dr Bassoe came to the leadership of the laboratory and clinic he was already ill and advanced in years

His medical writings include over 100 titles, the first one published in 1898, while an intern in the Cook County Hospital Probably the most important of them are his careful studies of caisson disease and of the triad of acromegaly, gigantism and dwarfism

In his last years he became interested in medical history and wrote useful accounts of the development of neurology and psychiatry in Chicago and the Middle West He had also become much interested in Mexico, he spent several vacations there and learned Spanish, and this led him to an interesting study of the early care of psychiatric patients in Spain

He was very sociable and loved to go to medical meetings, where his quizzical smile and

PETER BASSOE, M D
1874-1945 •

quaint drawl, which he never quite lost, were familiar He was no puritan and took a drink with the boys, but never more than he could hold, and, when the stories began to descend below the belt line, he would quietly transfer himself to a company which still retained its dignity Tolerance and moderation were his marked characteristics His early experiences at home gave him a distaste for public controversy He was a courageous man and staunchly supported his ideals but rarely did he make an open frontal attack His quiet scorn was sometimes effective, but his favorite method was simply to start something better An example of this approach is the founding of the Central Neuropsychiatric Association

In 1911 he was elected to the American Neurological Association, where he had a chance to see how that organization was dominated by the Atlantic seaboard The meetings were always held along the Atlantic coast, causing much inconvenience and expense to neurologists west of the Alleghanies This situation had often been discussed, but it remained for Bassoe to do something about it In St Louis, in 1922, he gathered a group of neuropsychiatrists and proposed the organization of a Central Neuropsychiatric Association, which should hold its meetings in rotation in various cities, thus making it possible for the membership to become better acquainted with the various clinics and so serve as a stimulus to the local group He was elected first president of the organization, which claims the allegiance of an increasingly friendly and enthusiastic membership, of which he was one of the most faithful

He was aware of the unsatisfactory conditions in the state hospitals for the insane in Illinois but did not tilt at windmills, like that Don Quixote of psychiatry, Clevenger He worked quietly and persistently, nevertheless, to improve conditions, being a member of Governor Horner's committee which drew the plans for the establishment of the Illinois Neuropsychiatric Institute After the affiliation of the Presbyterian Hospital with the University of Illinois, he promptly transferred his outpatient department to the Institute and faithfully attended its staff conferences

Dr Bassoe was primarily a physician—painstaking, solicitous and tireless in the care of his patients He examined them carefully and had an amazingly accurate memory for the details of their illnesses None needed to tell him that the physician must treat the patient as well as the illness, he knew this by instinct

His professional activity centered around the Presbyterian Hospital and the Central Free Dispensary, but he was, at one time or another, on the staff of numerous hospitals in Chicago and its vicinity, including the Rogers Memorial Sanitarium at Oconomowoc, Wis, of which he was a trustee During World War I he was a contract surgeon and later was consulting neuropsychiatrist of the United States Public Health Service, from 1918 to 1922

He was a modest man, yet many honors came to him In 1904 he was president of the Chicago Scandinavian-American Medical Association, in 1908, president of the Chicago Pathological Society, in 1911, president of the Chicago Neurological Society in 1922 president of the Central Neuropsychiatric Association and Chairman of the Section on Nervous and Mental Diseases of the American Medical Association, in 1927, president of the American Neurological Association, in 1930, president of the Association for the Study of Internal Secretions and in 1936, president of the Institute of Medicine of Chicago He was an honorary member of the Neurological Society of Norway and of the Swedish Medical Association

Peter Bassoe died of coronary thrombosis on Nov 5, 1945 He was universally beloved His friendly presence and sober counsel will be sorely missed by all who knew him He was the sort of able and honorable immigrant hundreds of whom came to this country in search of better opportunities than they could find in their homelands and remained to strengthen and enrich it Would that we had more of them!

PERCIVAL BAILEY, M D.

Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Anatomy and Embryology

NEUROSECRETION VI A COMPARISON BETWEEN THE INTERCEREBRALIS-CARDIACUM-ALLATUM SYSTEM OF THE INSECTS AND THE HYPOTHALAMO-HYPOPHYSIAL SYSTEM OF THE VERTEBRATES B SCHARRER and E SCHARRER, Biol Bull **87** 242, 1944

The hypothalamohypophysial system in vertebrates is in many respects similar to the pars intercerebralis–corpus cardiacum–corpus allatum system in insects In vertebrates, the hypothalamic nuclei innervating the pars nervosa of the pituitary gland contain secreting nerve cells In insects, the pars intercerebralis of the protocerebrum contains neurosecretory cells On the basis of these morphologic relationships, the hypothalamic nuclei and the pars nervosa of the hypophysis appear as one, closely interconnected system Likewise the pars intercerebralis and the corpus cardiacum of insects may be viewed as one neuroendocrine complex rather than as two separate sources of hormones

COBB, Boston

THE ARCHITECTURE OF THE CEREBRAL CAPILLARY BED IN LUNGFISHES E HORNE CRAIGIE, J Comp Neurol **79** 19 (Aug) 1943

Craigie examined microscopic sections of brain tissue from an African, an American and an Australian lungfish In the African and American forms he found a large-meshed capillary network, less complex than in most other fishes In the Australian fish, in addition to the network were capillaries in the form of hairpin loops The presence of the latter indicates that the Australian form is the most primitive of the three

ADDISON, Philadelphia

VISUOMOTOR COORDINATION IN THE NEWT (TRITURUS VERIDESCENS) AFTER REGENERATION OF THE OPTIC NERVE R W SPERRY, J Comp Neurol **79** 33 (Aug) 1943

It has been shown by Stone that normal vision may be recovered in adult urodele amphibians after reimplantation and transplantation of adult eyes Sperry has extended these observations in 58 adult newts by rotating the left eyeball 180 degrees on the optic axis, cutting the optic nerve and allowing regeneration Tests of vision were made on the tenth day after operation and twice a week thereafter The criteria of response used in judging vision included compensatory movements of the head to rotation of the visual field and visual localization of small moving objects In the great majority of cases visual responses to photic stimulation of the left eye reappeared about thirty days after section of the left optic nerve In all cases the recovered vision was systematically reversed and inverted, conforming to the rotated position of the retina Although the reversal proved to be a great handicap to the animal's activities, it persisted without correction

ADDISON, Philadelphia

THE RETICULAR NATURE OF GLIA FIBERS IN THE CEREBRUM OF THE FROG AND IN THE HIGHER VERTEBRATES WARREN ANDREW, J Comp Neurol **79** 57 (Aug) 1943

Andrew studied the brains of 30 frogs, prepared by the methods of Ramon y Cajal, del Rio Hortega and Penfield For comparison, tissues of the human brain prepared by Cajal's gold chloride-mercury bichloride method were used In the frog the glial framework was predominantly formed of processes of the ventricular ependymal cells Different regions showed a varying manner of distribution of the ependymal processes In some regions the fibers were seen as individual structures running from the ependymal cells to the pia mater, in other regions they had fine branches which anastomosed and appeared to form a true reticulum Study of the human cerebrum at high magnifications revealed very fine glial fibers which formed a continuous reticular framework These observations, however, do not enable Andrew to decide whether the finest fibers should be considered always as the most delicate branchings of the astrocytes or as a general reticular framework on which the astrocytes lie

ADDISON, Philadelphia

CHROMATOLYSIS AND RECOVERY OF EFFERENT NEURONS ROBERT STUART TURNER, J Comp Neurol **79** 73 (Aug) 1943

Turner cut the right sciatic nerve of 20 guinea pigs just below the ischial tuberosity The animals were allowed to live for varying lengths of time From one-half these animals he removed the fifth lumbar segment of the spinal cord fifteen days after cutting the sciatic nerve, and from the other half he removed this segment at periods ranging from seven months to two years The tissues were sectioned serially and stained with carbol thionin to show the cells Total counts of normal and of chromatolyzed motor cells in the spinal cord were made on the side of operation and on the side of the intact nerve As a control, Turner made counts of the total number of cells in the fifth lumbar segment of 13 guinea pigs not subjected to operation and found the two sides not significantly different Fifteen days after section of the sciatic nerve on one side about 38 per cent of the anterior motor horn cells on the side of operation showed chromatolysis The guinea pigs kept seven months to two years after section of the nerve showed about 16 per cent fewer anterior horn cells on the side of operation It is deduced that recovery took place in approximately two thirds of the motor cells which had undergone definite chromatolysis

ADDISON, Philadelphia

AN EXPERIMENTAL STUDY OF THE FACIAL NERVE JAMES O FOLEY and FRANKLIN S DUBOIS, J Comp Neurol **79** 79 (Aug) 1943

Foley and DuBois have made a quantitative and qualitative analysis of the functional components in the rootlets, trunk and branches of the facial nerve In

10 cats and 1 dog the somatic and visceral motor fibers were eliminated on the right side by sectioning the facial rootlets as they emerged from the pons or by a longitudinal cut of the pons in the region of the attached rootlets After fourteen days both the right and the left facial nerve and their branches were dissected out, and specimens were taken from eight or more regions These specimens were prepared with a silver technic to show fibers In addition, in 1 cat the auricular nerve was sectioned as it emerged from the jugular ganglion, and in another cat a superior cervical ganglion was removed A postoperative survival period of fourteen days was allowed these animals also, and the technic was the same as that employed with the others For comparison, sections of the facial nerve of a cat not subjected to operation were stained for myelin The somatic motor axons numbered on the average 9,000, the visceral motor axons, about 2,000, and the sensory fibers, 2,200 Of the visceral motor fibers, approximately 70 per cent were distributed in the great superficial petrosal nerve and 30 per cent in the chorda tympani Of the sensory fibers, about 36 per cent passed into the great superficial petrosal nerve, 50 per cent entered the chorda tympani, and 14 per cent passed peripherally in the trunk of the facial nerve Before emerging from the stylomastoid foramen, the facial nerve was joined by the auricular branch of the vagus nerve, which contained about 8,000 fibers In the cat it appears that the few sensory fibers of the facial nerve which are distributed superficially to the head accompany the auricular branch of the vagus nerve

ADDISON, Philadelphia

EXTENSIVE UNILATERAL CEREBRAL REMOVALS IN THE PRIMATE PHYSIOLOGIC EFFECTS AND RESULTANT DEGENERATION FRED A METTLER, J Comp Neurol **79** 185 (Oct) 1943

Mettler studied 9 monkeys after making unilateral lesions of varying extent on the left hemisphere From 3 of the animals he removed only portions of the cortex, from 1 animal he removed all the neocortex of the left cerebral hemisphere, and from 4 others, in addition to the cortex, he removed portions of the striate body In the ninth animal the entire left hemisphere was removed as far as the posterior commissure The activities of the animals were observed for varying periods, and finally histologic examinations were carried out For each animal copious physiologic and histologic data are given, and a chart presenting data on the 7 principal subjects allows a quick comparison of important physiologic conditions, such as the patellar reflex, the plantar reflex, monomanual and bimanual feedings, posture of the right arm, direction of circling movements and resistance to passive movement Mettler observes that in this series of progressively extensive unilateral cerebral removals there was gradual degradation of motor performance rather than paralysis Spasticity was more conspicuous after combined cortical and subcortical damage than after cortical damage alone Resistance to passive movement was first seen when the pallidum as well as the cortex was involved From study of the sections of these brains, together with supplemental information from various other investigators, Mettler has constructed a series of thirty-six diagrams, which collectively present a working plan for the principal connections of the thalamic nuclei Half these diagrams are the same as those in Mettler's "Neuroanatomy" (St Louis, C V Mosby Company, 1943) Of the cortical fibers to the striatum, approximately one half come from the frontal cortex and the other half from the nonfrontal cortex Only about one half of all the fibers from the frontal region originate in area 4 The compact part of the substantia nigra sends fibers to the pallidum, while the diffuse and lateral parts of the substantia nigra appear to discharge on the striatum The pallidum receives fibers from the centromedian nucleus This circuit appears responsible for some of the more complex patterns of associated movements

ADDISON, Philadelphia

Physiology and Biochemistry

OBSERVATIONS ON MUSCLE SPASM IN POLIOMYELITIS ELECTROMYOGRAPHIC STUDIES ON EFFECT OF VARIOUS FORMS OF THERMAL THERAPY AND OF PROSTIGMINE A L WATKINS and MARY A B BRAZIER, Arch Phys Therapy **26** 325 (June) 1945

Hypersensitivity or spasm of muscles has been emphasized as one of the most characteristic aspects of the acute stage of poliomyelitis Watkins and Brazier studied the influence of single applications of a therapeutic agent on muscle spasm during the first weeks of the disease All patients were in the early infectious stage, and studies were restricted to adult patients Six such patients were available for study In all, 835 measurements were made, the first test usually being made within a few days after diagnosis had been established Muscle spasm was measured by quantitation of the electrical discharges released on five seconds of passive stretching by known weights in order to test the effect of twenty minute applications of hot packs, infra-red radiation, luminous heat, short wave diathermy and the intramuscular injection of neostigmine (1 6 mg) on this electrical component of spasm Single applications of hot packs, infra-red radiation and diathermy had no effect Luminous heat and neostigmine caused a decrease in spasm of approximately 25 per cent This degree of change was not great enough to indicate a specific effect on spasm

J A M A

Neuropathology

TUMORS OF THYMUS IN MYASTHENIA GRAVIS N A MURRAY and J R MCDONALD, Am J Clin Path **15** 87 (March) 1945

Murray and McDonald studied thymus glands removed from 10 fetuses and from 100 persons from the ages of 4 months to 86 years They also studied thymomas associated with myasthenia gravis in 13 cases and thymic tumors removed surgically in 2 cases of myasthenia gravis Several observations made by them suggested that these tumors are thymomas Most primary tumors of the thymus associated with myasthenia gravis are of a single type They are made up of lymphocytes and of larger pale cells with faintly acidophilic cytoplasm in varying proportions and indefinite cell boundaries These tumors contain numerous small blood vessels and occasional Hassall corpuscles A "lining up," or palisading, of the pale cells along connective tissue trabeculae and pseudorosette formation around blood vessels appear to be distinguishing features If metastasis and direct extension are sufficient criteria for the diagnosis of malignancy, then these tumors are malignant It is believed that "thymoma" is an adequate name for tumors of this type The tumors which will metastasize cannot be distinguished from those which will not metastasize The absence or presence of secondary germ centers (lymph follicles) does not point either to or away from malignancy The

absence of differentiation of cortex and medulla is not a reliable criterion for the diagnosis of malignancy The incidence of myasthenia gravis among patients with thymoma is nearly 100 per cent Eaton has stated that the incidence of thymomas among patients with myasthenia gravis is 14 per cent According to Bell, the incidence at necropsy of thymic dysplasia among patients who have died of myasthenia gravis is about 50 per cent J A M A

ALTERATIONS IN STRUCTURE OF MOTOR NERVE-ENDINGS IN SKELETAL MUSCLE OF RABBITS WILLIAM B DUBLIN, J Nerv & Ment Dis **100** 275 (Sept) 1944

By means of the gold chloride method, Dublin studied the structure of motor nerve endings in skeletal muscle of normal rabbits and in rabbits after curarization, hypothermia and exercise There was considerable variation in the structure of the nerve endings in the untreated animals No remarkable alteration was seen in the motor nerve endings of curarized muscle, although slight contraction of the endings was observed After hypothermia induced by packing in ice rabbits lightly anesthetized with a barbiturate, there was no appreciable change in the motor nerve endings as studied in biopsy specimens After exercise the motor nerve endings were observed to be expanded

CHODOFF, Langley Field, Va

A NEW METHOD FOR IMPREGNATION OF OLIGODENDROGLIA AND MICROGLIA IN ORDINARY NECROPSY MATERIAL ANTONIA GRIÑO, J Neuropath & Exper Neurol **4** 93 (Jan) 1945

Griño describes a staining technic for the impregnation of oligodendroglia and microglia in specimens which have been subjected to the conditions of routine autopsy and fixed in solution of formaldehyde U S P (1 4) from fifteen days to one year The frozen sections are treated with an oxidizing agent and the cells impregnated with an ammoniacal solution of silver tungstate, followed by reduction in solution of formaldehyde U S P

The author states that when this method is properly employed it is specific for oligodendroglia, microglia, their expansions and the adventitial cells of the vessels Astrocytes and neurons are not brought out Other organic and inorganic salts of silver (arsenate, molybdate, oxalate, citrate, etc) were tried, without good results Griño mentions the possibility that oligodendroglia and microglia may possess definite avidity for oxygen No conclusions were drawn as to the mechanism of impregnation with silver compounds

GUTTMAN, Philadelphia

DEATH FROM ELECTRICAL CONVULSION THERAPY F J NAPIER, J Ment Sc **90** 875 (Oct) 1944

Napier describes 5 civilian deaths resulting from shock treatment A sixth has been reported, but no details are available These are the only known deaths from this cause in England and Wales since the treatment was started

Of the 5, only 2 deaths resulted directly from the convulsion Of these, 1 death was due to a hemorrhage involving both lobes of the thyroid gland and filling the mediastinum Death occurred six hours after treatment, with only a little restlessness and ten minutes of dyspnea as a warning This was the first shock treatment given the patient, who had had toxic diffuse goiter twenty-one years before but showed no abnormal physical signs on admission other than pallor The other death directly attributable to shock was that of a 65 year old man with a blood pressure of 185 systolic and 90 diastolic, slight enlargement of the left ventricle and heart sounds of poor quality Urinalysis revealed a specific gravity of 1 010, a trace of albumin and the presence of pus cells on one occasion The patient was given five shocks without convulsion The first, and last, convulsion resulted in acute collapse and death one-half hour later There was pronounced relative preponderance of the left ventricle, and the myocardium was extremely soft

Of the patients whose deaths did not directly follow shock, 1 fractured the acetabulum during the second treatment and died of pulmonary tuberculosis six months later Another died in uremia after a fracture of the femur incurred during the third treatment Another had bronchopneumonia six days after the second treatment and died four days later Postmortem examination showed bronchopneumonia and chronic nephritis in the last 2 cases McCARTER, Boston

THE SPINAL FLUID IN HEINE-MEDIN DISEASE (ACUTE ANTERIOR POLIOMYELITIS) A M MARQUE, J M MACONI and C R GIUDICE, Rev neurol de Buenos Aires **9** 248 (July-Sept) 1944

The authors report on the analysis of 129 specimens of spinal fluid taken in cases of anterior poliomyelitis during the epidemics of 1936 and 1942 The fluid was always clear, without xanthochromia, blood or spontaneous coagulation The Pandy reaction was positive in 37 per cent of the specimens, it was usually negative in cases in which the illness was of less than fifteen days' duration Pleocytosis, characteristic of all cases, was most pronounced during the first few days and in the week following the appearance of paralysis No relation was observed between the intensity of the disease, the types of paralysis and the number of cells in the fluid The highest number of cells was 600 per cubic millimeter, on the sixth day, in a boy of 5 years with paraplegia, the lowest number of cells was 6 4 cells per cubic millimeter, on the eighth day, in a girl of 2½ years with paraplegia The cells gradually diminished in number They were mainly lymphocytes, with polymorphonuclear leukocytes in some cases The authors failed to observe the predominance of polymorphonuclear leukocytes during the first twenty-four to forty-eight hours, as reported by Peabody An increase in protein content was observed in almost all cases, especially during defervescence and after paralysis set in, the amount varied from 50 to 200 mg per hundred cubic centimeters The sugar was usually increased, except in 1 case (34 mg per hundred cubic centimeters) There were no significant changes in the chloride content, which varied from 640 to 819 mg per hundred cubic centimeters The colloidal gold curve was normal in 38 per cent of the cases, in 62 per cent the curves were atypical The Guillain test was made in 32 cases, with precipitation in the second zone in most cases The Wassermann reaction was negative in all cases

SAVITSKY, New York

SECONDARY EFFECTS OF QUINACRINE [ATABRINE] ON NERVOUS SYSTEM H VOLLMER and H LIEBIG, Deutsche med Wchnschr **70** 415 (July 21) 1944

Experiments on rabbits and cats revealed certain secondary effects of quinacrine on the central nervous

system of these animals Psychosis and motor excitement were caused by suicidal attempts with large doses of quinacrine hydrochloride (1 9 to 9 Gm) Vollmer and Liebig report 4 cases of recurrent tertian malaria in which secondary effects on the central nervous system were observed The occurrence of these reactions was not in agreement with the observations of other authors, who have asserted that reactions of this type do not result from the administration of therapeutic doses of the drug The incidence (4 in 450 cases) was low Psychosis resulted in 3 cases from intramuscular injection of quinacrine, and psychosis associated with bulbar paralysis and flaccid paralysis of the lower extremities, in 1 case The aforementioned disturbances were of short duration There were no cases of irreversible effects

J A M A

Psychiatry and Psychopathology

NEUROPSYCHIATRIC CASUALTIES FROM GUADALCANAL I PERSISTENT SYMPTOMS IN THREE CASES ALBERT A ROSNER, Am J M Sc **207** 770 (June) 1944

Rosner reports the cases of 3 typical American soldiers, 27, 23 and 20 years of age, respectively, with diverse sociologic and geographic origins They were of normal emotional and psychologic makeup, with no family histories of mental disorder Their fundamental patterns of reactivity had been considered normal in the past, but after the shattering experiences at Guadalcanal they manifested such grave behavior disturbances that they became unfit for military duty Of interest was the fact that their symptoms and complaints were similar For example, such expressions as "It's too much for me, I get nervous when I get out there and have to give orders, I can't do it" or "I feel weak and I have no energy," were typical of the conditions All had been exposed to extreme exhaustion, fear, hunger, thirst, tropical heat and humidity, and jeopardy of life and limb Although 2 of them had been rendered unconscious as a result of shell bursts, there were no postconcussion symptoms or amnesia One year later symptoms still persisted despite active therapeutic measures

MICHAELS, M C, A U S

UNUSUAL REACTIONS TO ELECTROSHOCK CARROLL W OSGOOD, J Nerv & Ment Dis **100** 343 (Oct) 1944

A survey was made of all unusual reactions of patients treated with electric shock in an attempt to answer questions as to the safety and effectiveness of this method of treatment The reactions are divided into two groups those which appear in the treatment room and those which present themselves as later reactions It has been suggested that petit mal seizures, generally agreed to be ineffectual, may be harmful No patients in the survey who were prone to petit mal attacks showed any ill effects, although they demonstrated rather less than average improvement The panic reaction seems to be characteristic for a given patient, but it may be modified by medication before treatment Repetitive speech lasting for an abnormal period, without apparent ill effect, was observed

Among the later reactions are increased restlessness or agitation without much clouding, dazed retardation and states of excitement and uncooperativeness These reactions, although occasionally alarming, had no untoward effects on the progress of the disease The author believes that while patients may be made temporarily worse mentally, as well as being subjected to certain physical hazards, and while their psychoses may be activated or may progress in spite of treatment, they are seldom, if ever, made permanently worse

CHODOFF, Langley Field, Va

THE PROGNOSTIC VALUE OF CLINICAL FINDINGS IN CASES TREATED WITH ELECTRIC SHOCK LEONARD GOLD and CARMELO J CHIARELLO, J Nerv & Ment Dis **100** 577 (Dec) 1944

Gold and Chiarello studied the relation between the results of electric shock therapy and certain individual clinical observations in 121 consecutive male patients Of the total, 20 per cent showed "much improvement," 22 per cent "improvement," 15 per cent "improved behavior" and 42 per cent no change Indicative of a good prognosis prior to treatment was a symptom complex of muteness, perplexity and confusion, fear of an immediate personal threat or danger, and depression Patients in the age groups of 11 to 20 and 51 to 60 years did better than those in the intervening period Other favorable factors were duration of illness of less than one year, sudden onset, exogenic precipitating factors, good marital and sexual adjustments and a background of familial stability Factors portending a poor prognosis were gradual onset, long duration of illness, previous shock therapy, gradual loss of interest, negativism, restlessness ideas of reference and grandiose delusions The authors believe that detailed examination of individual symptoms is more important in prognosis than the categorizing of patients into formal diagnostic groups

CHODOFF, Langley Field, Va

PEPTIC ULCERS IN THE INSANE O J POLLAK and F KREPLICK, J Nerv & Ment Dis **101** 1 (Jan) 1945

Pollak and Keplick, in an analysis of the frequency with which peptic ulcer was observed in 2,000 necropsies performed on patients with mental disease from a state hospital, found an incidence of 2 1 per cent No significant correlation was noted between the presence of peptic ulcer, on the one hand, and the type of insanity, the character of the mental symptoms or the sexual adjustment of the patient, on the other More than one-half the patients displayed a prepsychotic mental makeup of the type commonly encountered in nonpsychotic patients with ulcer No undue predominance of either the asthenic or the hypersthenic type of body build was found to be associated with the occurrence of ulcer One third of the patients had multiple ulcers, as compared with the usually reported figure of 5 to 10 per cent The incidence of ruptured ulcer in 13 patients (31 per cent) is explained partly on the basis of the visceral atony often present in psychotic patients In 12 patients the ulcers proved fatal, although only a small number presented symptoms of ulcer during life

CHODOFF, Langley Field, Va

Meninges and Blood Vessels

A CASE OF ACUTE MENINGITIS CAUSED BY NEISSERIA PERFLAVA LAWRENCE H SOPHIAN, Am J M Sc **207** 376 (March) 1944

Sophian reports the case of a 31 year old merchant seaman who was admitted in an acutely ill condition He had hallucinations, tremor, a history of recent alcoholic intoxication, Babinski, Oppenheim and Gordon signs on the left side, a partial Babinski sign on the right side, and a Brudzinski sign bilaterally There was extreme rigidity of the neck, and the Kernig sign

was positive The patient responded only to painful stimuli

A spinal tap showed an initial pressure of 220 cm and a cell count of 15,000 leukocytes, mostly neutrophils, per cubic millimeter The organisms found appeared larger than the usual strain of Neisseria intracellularis

Autopsy revealed a very thick, greenish yellow exudate closely attached to the base of the brain, extending from the optic chiasm to the medulla The thickest exudate was localized around the pituitary gland Microscopic examination showed an unusually dense accumulation of neutrophils in the pia and arachnoid The causative organism was found to be Neisseria perflava The portal of entry found at autopsy, was a congenital defect in the roof of the sphenoid sinus

MICHAELS, M C, A U S

THE EVALUATION OF ALCOHOL LUMBAR PARAVERTEBRAL BLOCK IN PERIPHERAL VASCULAR DISEASE GAMALIEL SALAND and CHARLES KLEIN Am J M Sc **207** 749 (June) 1944

Saland and Klein studied 16 patients who applied to the vascular clinic for relief of symptoms The patients were treated by paravertebral block temperature readings at the surface of the skin were taken one hour before injection to allow the temperature of the skin to stabilize Follow-up temperature readings of the surface of the skin were made at various intervals during the first three days and subsequently at longer intervals A difference in temperature of 2 C in corresponding areas of the extremities was considered significant Five patients showed complete immediate vasodilatation, lasting three to one hundred and eight days, 9 patients showed an immediate or delayed significant vasodilatation, lasting three days to two years Neuritis was produced when a larger amount of alcohol was injected In no instance did the neuritis last longer than forty-five days Of 10 of the 12 patients with peripheral vascular disease, 5 showed improvement, three showed no change and 2 were definitely worse There was no correlation between claudication time and the degree of vasodilatation

MICHAELS, M C, A U S

SALMONELLA CHOLERAE SUIS MENINGITIS ERWIN R NETER, Arch Int Med **73** 425 (May) 1944

Neter reports the case of a white girl aged 3 years and 11 months who was blind and hydrocephalic Bacteremia and meningitis developed Cultures of the blood and the cerebrospinal fluid revealed the presence of many gram-negative bacilli, which were identified as Salmonella cholerae suis (Salmonella suipestifer) Examination of the feces failed to reveal paratyphoid bacilli The serum of the patient failed to show the presence of specific agglutinins Sulfadiazine therapy was instituted, but in spite of this treatment the child died the following day Cultures of the stools of the child's father, mother and brother failed to show evidence of paratyphoid bacilli, and agglutinins against the patient's strain could not be demonstrated in their serum

The author reviews 78 cases of Salmonella meningitis described during the past twenty years Twelve different species and types of Salmonella have been encountered in the past as the causative agent These represent only a fraction of the species known to be pathogenic to man Not a single case of meningitis due to the paratyphoid A bacillus is included in the group Members of group B of the genus Salmonella account for 26, or one third, of all cases Only 5 cases of meningitis were caused by Salmonella cholerae suis, the sole representative of group C—more than one half of all instances of Salmonella meningitis were due to members of group D Group E is represented by Salmonella sp (London type) in a single case

The author concludes that the prognosis of Salmonella meningitis is poor, but a few cases with recovery have been reported No conclusions with respect to the efficacy of sulfonamide compounds can as yet be drawn, and they are not equally effective toward all species and types of the genus Salmonella

GUTTMAN, Philadelphia

THROMBOPHLEBITIS OF A CAVERNOUS SINUS FOLLOWING EXTRACTION OF TEETH IRVING H WIESENFELD and EDWARD PHILLIPS, Arch Otolaryng **40** 497 (Dec) 1944

Wiesenfeld and Phillips report a case of thrombophlebitis of the cavernous sinus in which recovery followed treatment with penicillin and heparin The patient, an 18 year old white youth, had bilateral maxillary sinusitis Conservative treatment was advised, but when pain developed in the upper teeth on the right side, a dentist extracted the right upper first bicuspid, as well as a supernumerary tooth which lay alongside the bicuspid and which was impacted in the hard palate The extraction was performed with difficulty The patient was next seen two days after the extraction, when he appeared acutely ill Cellulitis of the right cheek was obvious, and the temperature was 102 F Sulfadiazine treatment was begun Two days later the patient was hospitalized, and cultures of the pus from the draining tooth socket revealed Staphylococcus aureus The dose of sulfadiazine was increased until the level of the drug in the blood ranged from 9 6 to 12 8 mg per hundred cubic centimeters In spite of this, the infection spread, and one week later a diagnosis of thrombophlebitis of the right cavernous sinus was established There was palsy of all the extraocular muscles on that side, and the disk was found to be choked to 8 D Several hours later proptosis of the left eye developed, and 4 D of papilledema was present The patient seemed moribund, when penicillin therapy was instituted A continuous intravenous drip of penicillin and heparin was started and continued for eleven days The dosage of heparin was adjusted to maintain the clotting time at approximately fifteen minutes A total dose of 2,000,000 units of penicillin was given in twenty days, the drug being administered intramuscularly during the last nine days

The case is illustrative of the well known dangers of operation on oral structures in the presence of acute infection It is assumed that the staphylococcic infection was refractory to the sulfadiazine and that recovery of the patient was due to penicillin The role of heparin in the recovery is difficult to evaluate

RYAN, Philadelphia

MENINGOENCEPHALITIS IN LYMPHOGRANULOMA VENEREUM CHRIS J D ZARAFONETIS, New England J Med **230** 567 (May 11) 1944

Zarafonetis reports on 2 patients with lymphogranuloma venereum Both had complaints of headache, and 1 had a five day period of amnesia followed by confusion for about seven days Manometric studies revealed a persistent block of the subarachnoid space Both patients gave positive reactions to complement fixation tests and the Frei test, and a virus was isolated

from an inguinal lymph node of 1 patient five months after the onset of his illness The observations on these patients indicate that lymphogranuloma venereum may produce meningoencephalitis, as well as myelomeningoencephalitis with adhesive arachnoiditis

GUTTMAN, Philadelphia

MENINGOGENIC REFLEX MYRINGITIS FELIPE CORA ELISEHT and JUAN MONTERO, Prensa med argent **31** 2652 (Dec 27) 1944

In October 1944, a paper on "reflex myringitis" of meningeal origin by Marinho appeared in a Brazilian journal Marinho stated that this was an early sign of meningeal irritation in nonotogenic involvement of the meninges Ferrari had described hyperemia of the tympanic membrane as an early sign of tuberculous meningitis Marinho described the sign as a reddening of the tympanic membrane with an intact cone of light and no blurring of the landmarks In occasional cases the congestion becomes so marked as to cause blurring of the anatomic landmarks The authors state that they looked for this sign described by Marinho in cases of nonotogenic meningitis, hemorrhagic pachymeningitis and head traumas, but they were unable to find it They indicate the difficulty in ruling out infections of the middle ear as the cause of the changes in the tympanic membrane

SAVITSKY, New York

MENINGEAL APOPLEXY A FORTES, Rev mex de psiquiat, neurol y med leg **9** 17 (Jan) 1945

Fortes reports 2 cases of subarachnoid hemorrhage The first was that of a 36 year old white man whose illness began with sudden, intense frontal headache, followed by loss of consciousness Right hemiplegia was found on his admission to the hospital The author does not mention meningeal signs The patient was in a stupor The right internal carotid artery was ligated, and a trephination was done in the left temporal region, 20 cc of blood was aspirated After the operation the hemiplegia disappeared As the patient recovered from stupor, aphasia, agraphia and alexia developed Three months after the operation he had an epileptic attack and showed a mild residual aphasic defect

The other case was that of a 40 year old white woman whose illness also began with sudden, severe pain in the head and transitory loss of consciousness, preceded for a short time by paraesthesias in all the limbs On admission to the hospital, the patient showed generalized increase in the tendon reflexes No signs of meningeal irritation are mentioned The right internal carotid artery was ligated The pain disappeared, and the patient's condition cleared up fourteen days after the operation

SAVITSKY, New York

Diseases of the Spinal Cord

X-RAYS IN DIAGNOSIS OF POSTERIOR HERNIATION OF INTERVERTEBRAL DISK A E CHILDE, Canad M A J **52** 458 (May) 1945

At the Montreal Neurological Institute and at the No 1 Canadian Neurological Hospital various methods have been used to diagnose herniation of the intervertebral disks Since early in 1942 the injection of iodized oil, with subsequent aspiration, has become routine During part of this period iodized poppyseed oil has been the medium, but Pantopaque is much to be preferred, not only because it is much more easily injected and aspirated but because it moves more freely There is the additional advantage that any small amount which may be left in place is gradually spontaneously absorbed While it is not as radiopaque as iodized poppyseed oil, it is sufficiently dense for practical purposes Childe stresses that plain roentgenograms should always be made first These films usually are not diagnostic of such a herniation but may offer suggestive evidence, and they help to exclude other lesions Myelographic examination when properly performed using Pantopaque with subsequent aspiration is an accurate and safe method Multiple herniations of the disks are not uncommon, and many unsatisfactory results may be explained on this basis if operation is undertaken without previous myelographic studies Herniation of sufficient size to produce great disability may cause only comparatively small deformities of the subarachnoid space Hence the use of a relatively large quantity of oil is advisable, and multiple spot films should be made routinely to avoid missing minor deformities not readily seen under the fluoroscope Myelographic study reveals that the size of some herniations undergoes change, owing to such factors as weight bearing, traction, muscular activity, flexion and extension Herniated intervertebral disks in the cervical region are often complicated by hypertrophic bone formation Tumors in the lumbar and sacral regions, and occasionally in the cervical region, may produce signs and symptoms which are clinically indistinguishable from those produced by herniated intervertebral disk Myelographic examination will usually differentiate between a tumor and a herniated disk

J A M A

Peripheral and Cranial Nerves

TOTAL HERPES ZOSTER OF THE OPHTHALMIC, MAXILLARY AND MANDIBULAR DIVISIONS OF THE TRIGEMINAL NERVE HUGH O'NEILL, Arch Ophth **33** 237 (March) 1945

Herpes zoster ophthalmicus, or herpes zoster of the gasserian ganglion, is rare Indeed, it is so rare that Rice stated that no cases of ophthalmic herpes zoster were mentioned, for example, in the report of one of the largest ophthalmologic and otologic hospitals in the United States, in which over 100,000 patients with ocular disease were treated in 1922 On the other hand, Gundersen, in searching for cases of herpes zoster ophthalmicus, found 10 per annum at the Massachusetts Eye and Ear Infirmary, in Boston, over a five year period

Herpes zoster involving the ophthalmic, maxillary and mandibular divisions of the fifth cranial nerve is rare, judged by the absence of reported cases in the literature Herpes zoster of the trigeminal nerve with concomitant cutaneous involvement of the geniculate ganglion, the combination of which likewise has not been reported in the literature, is rare indeed, although Fuchs, cited by Graves, reported 2 cases in which with herpes zoster ophthalmicus there was concurrent involvement of the seventh cranial nerve, with resulting lagophthalmos and keratitis This combination is not rare, nor is that of herpes zoster ophthalmicus with involvement of the third, fourth, sixth and seventh cranial nerves, with ocular palsy

O'Neill reported a case of partial herpes zoster of the seventh cranial nerve, involvement of the vestibular ganglion of the eighth cranial nerve and complete herpes zoster involving all three divisions of the trigeminal nerve On account of the severe pain, the ocular involvement and the residual scarring on the cutaneous

branches of the trigeminal nerve, a diagnosis of herpes simplex or of herpes febrilis was inadmissible The ocular signs included optic neuritis, exophthalmos, keratitis profunda and probable mild involvement of the third, fourth and sixth cranial nerves No evidence for classifying this case as one of symptomatic herpes zoster arising from encephalitis, syphilis, tuberculosis, leukemia Hodgkin's disease, hemorrhage in the cerebellopontile angle or cerebral tumor was found On the other hand, in view of the severe pain and the cutaneous herpetiform manifestations the case was obviously one of idiopathic herpes zoster of the fifth (complete), seventh (partial) and eighth (vestibular) cranial nerves

SPAITH, Philadelphia

UNUSUAL RAPID EVOLUTION IN GUILLAIN-BARRE SYNDROME WITH BULBAR PALSY ARTHUR A BRISKIER, J Nerv & Ment Dis **100** 462 (Nov) 1944

Briskier reports a case of the Guillain-Barre syndrome in a 40 year old man with a fatal termination eighteen hours after his admission to the hospital Unusual features of the case were the very rapid evolution and the widespread involvement of the central nervous system No causative organism was identified

CHODOFF, Langley Field, Va

RETROBULBAR OPTIC NEURITIS R A GREEVES, Lancet **1** 715 (June 3) 1944

Greeves lists three signs and symptoms associated with acute retrobulbar optic neuritis besides the central scotoma These are (1) partial dilatation of the pupil, which reacts to light but does not hold the reaction, (2) a sensation of pain when the eyeball is moved, and (3) tenderness of the globe to pressure He feels that the last is found usually only with pressure on the upper surface of the eyeball and is sensed by the patient as though in the midline of that structure The pupillary reaction described is the most frequently found of the three, but even this may be absent or anomalous

MCCARTER, Boston

Treatment, Neurosurgery

RAPID TREATMENT OF NEUROSYPHILIS WITH MALARIA AND CHEMOTHERAPY BERNHARD DATTNER, EVAN W THOMAS and GERTRUDE WEXLER, Am J Syph, Gonor & Ven Dis **28** 265 (May) 1944

Dattner, Thomas and Wexler report their experiences in treating patients with acute neurosyphilis The clinical material consisted of 419 patients with neurosyphilis who were treated with malaria followed by antisyphilitic chemotherapy Five of the patients were retreated with a different strain of malaria Of 424 courses of malarial therapy, 148 consisted of eight paroxysms followed by routine chemotherapy and 276 of eight paroxysms followed by administration of oxyphenarsine hydrochloride, 0 06 Gm each day, for ten days Of the 419 patients (424 treatment courses), 10 died, 62 could not be reached for follow-up observation, and 54 were too recently treated for evaluation of the effects of therapy Therefore, data on the results of therapy are limited to 293 patients, or 298 treatment courses The follow-up study included observations on 82 per cent of all patients, and the follow-up period extended from six to forty-eight months after the cessation of treatment

The authors could not observe any significant difference in the therapeutic results in the two groups They state that satisfactory results, as shown by examination of the cerebrospinal fluid, were obtained in 85 9 per cent of the patients

Dattner, Thomas and Wexler stress the fact that the increase in cells and protein in the cerebrospinal fluid, in addition to a positive Wassermann reaction, furnishes the best guide to selection of patients for effective fever therapy The authors conclude that "when the spinal fluid findings are used as a guide, prolonged chemotherapy following malaria is considered unnecessary and unwise"

GUTTMAN, Philadelphia

SENSITIZATION TO THIAMINE HYDROCHLORIDE WILLIAM STEIN and MATES MORGENSTERN, Ann Int Med **20** 862 (May) 1944

Stein and Morgenstern report the case history of a man who was addicted to alcohol and who had an entirely negative history for allergy He received seven injections of thiamine hydrochloride (15,000 to 20,000 international [U S P] units) during a four month period Approximately fifteen minutes after each treatment he suffered from severe pruritis and a large reddened wheal at the site of the injection These phenomena persisted for several hours About one month after the seventh injection the patient received 30,000 international units of thiamine hydrochloride by vein About thirty seconds later the patient experienced local, and then generalized, pruritis He became weak, cold and clammy, very dyspneic, cyanotic and eventually unconscious The pulse was rapid and thready Epinephrine hydrochloride (1 1,000), 0 3 cc, and caffeine and sodium benzoate, 0 5 Gm, were given subcutaneously About three hours later the reaction had almost completely subsided, and the following day the patient had completely recovered About forty-eight hours after this episode the patient exhibited a positive reaction by intradermal test with the original solution of thiamine hydrochloride

The authors report the case as the third recorded instance of sensitization to thiamine hydrochloride They conclude that intradermal testing with thiamine hydrochloride is advisable, prior to its parenteral administration, particularly when the patient has previously received parenteral thiamine hydrochloride

GUTTMAN, Philadelphia

SUDDEN "EXHAUSTIVE" DEATH IN EXCITED PATIENTS N R SHULACK, Psychiatric Quart **18** 3 (Jan) 1944

Shulack discusses mechanisms of sudden exhaustive death in excited patients He points out that such death may come very quickly and may be expected in hyperactive patients in the presence of a rapid, thready pulse, profuse perspiration and increasing hyperpyrexia He postulates that in these patients there is marked peripheral vasodilatation and a positive potassium balance Treatment consists in the following measures (1) maintenance of nourishment, body glucose and water to replace that lost from perspiration, through tubal feedings, rectal drip, veniclysis and hypodermoclysis, (2) subnarcosis (barbiturates, paraldehyde) to reduce general toxemia due to exhausting metabolic products, (3) replacement of sodium (oral or parenteral administration of sodium chloride), (4) low potassium diet, and (5) repeated intravenous administration of adrenal cortex extract (desoxycorticosterone acetate) or Escahatin

(adrenal cortex extract) in doses of 1 cc three times a day until the condition begins to improve, and a daily single dose until the patient is out of danger of exhaustion

Four cases are described The 2 patients who did not receive large doses of sodium chloride and adrenal cortex extract died, and the 2 who received sodium chloride desoxycorticosterone acetate or Eschatin lived

McCarter, Boston

Use of Metrazol in Barbiturate Poisoning Sirge Androp, Psychiatric Quart **18** 13 (Jan) 1944

Androp discusses the various analeptics used in treatment of barbiturate poisoning picrotoxin, metrazol, ephedrine and strychnine The first two drugs are the most important because the most efficacious Picrotoxin acts more slowly, and its effect is more prolonged But since the effect is cumulative, there is the danger that the dose given for an immediate therapeutic effect may later cause convulsions Metrazol acts quickly and to a maximum degree at once Both drugs have a selective stimulating action on the centers depressed by the barbiturates, particularly the respiratory center

The author reports the case of a 36 year old man with catatonia who rushed into the ward office, snatched a bottle of sodium amytal from the nurse and swallowed all its contents (102 grains [7 2 Gm]) He was treated with intravenous injections of metrazol, 36 cc being given in divided doses over the next six hours He recovered, without untoward results Elimination of the amytal was aided by high enemas and intravenous injections of dextrose and saline solution

The author warns that one must keep an ever-watchful attitude in cases of catatonic schizophrenia In spite of the seeming oblivion, catatonic patients do receive impressions of events and life about them, as attested recently by patients after shock therapy It is also suggested that no more sedatives and hypnotics be kept in the ward than is necessary for daily consumption

McCarter, Boston

Sleep-Electro-Shock Therapy H S Rubinstein, Science **101** 430 (April 27) 1945

Rubinstein reports on the administration of an aqueous solution of pentothal sodium prior to electric shock therapy, which can be given while the patient is asleep This method can be used in treatment of patients who refuse to continue with the therapy because of fear and persons for whom psychomotor excitability, as manifested by excitement, agitation, restlessness, shouting and combativeness, is undesirable

Guttman, Philadelphia

ILLINOIS PSYCHIATRIC SOCIETY AND CHICAGO NEUROLOGICAL SOCIETY

DAVID SLIGHT, M.D., *Presiding*

Joint Meeting, Jan. 6, 1945

Aleutian Paradox: Psychoneurotic Malingering. COMDR. A. R. MACLEAN (MC), U.S.N.R.

War Neuroses. LIEUT. COMDR. L. A. SCHWARTZ (MC), U.S.N.R.

What is a war neurosis? All are agreed that the usual psychoneuroses encountered in peacetime should not be termed war neuroses simply because they occur in a war setting. When these conditions are excluded, a group of cases is left in which the disturbance does not conform entirely to the nosologic criteria of psychoneuroses and which can be classified as such only with some difficulty. It is this group of cases in which I am interested, cases actually presenting a question of psychoneurotic symptoms in previously stable persons more than one of true psychoneuroses. One is confronted at once with the problem of what to call this disturbance and how to delineate clearly the syndrome variously called "war neurosis," "traumatic neurosis" and, of late, "combat fatigue."

The characteristic symptom of the "traumatic neurosis" is undoubtedly the "repetitious catastrophic nightmare." In its absence the diagnosis is suspect. Closely following the nightmare in frequency is the "startle reaction," produced by sudden loud noises and accompanied with physiologic evidence of anxiety, tremor, dilated pupils, sweating, dry mouth, flushing or pallor, palpitation and, in acute conditions, actual panic. Accompanying these symptoms are "a subtle personality change" which at times suggests the facies of schizophrenia and a guilt reaction with emotional depression.

There are, therefore, four arbitrary criteria for the diagnosis of "war neurosis," or "combat fatigue": first, a stable personality prior to the appearance of the traumatically determined emotional disturbance; second, combat experience of sufficient intensity to render it feasible as a precipitating agent; third, objective evidence of subjective anxiety, and, fourth, recoverability.

As an etiologic factor in the "traumatic neurosis," the personality is chiefly of importance in determining the severity of the neurotic symptoms under a given stimulus. In this connection, one finds two personality types—the emotionally and intellectually immature person, and the fully matured, independent older man—which appear to be of greatest importance in predisposition and which suggest a poor prognosis. Of more direct importance in the production of symptoms is the setting of interpersonal relationships in which the traumatic event occurs. In the patient's own story of the precipitation of the neurosis, four factors have occurred, singly or grouped, in too great frequency to be ignored: first, his having entered combat without faith and confidence in his leader; second, his having been insufficiently trained; third, his having entered combat surrounded by new shipmates, whose conduct under fire he had not had time to estimate, and fourth, his having experienced the combat situation when he was suffering with great physical fatigue.

It is believed that these four factors can be controlled to some extent and thus utilized in the prevention of "war neurosis" or "combat fatigue." Two other observations concerning the etiologic factors are of special therapeutic importance. 1. The difficulty in returning a patient to combat duty is increased in direct proportion to the distance to the front from which the patient has been evacuated. 2. All symptoms are liable to aggravation in the presence of loved ones, friends, relatives, spouse and family.

The preventive treatment of combat fatigue has been clearly indicated in the foregoing discussion. Active therapy consists in rest and emotional desensitization. Men should be given a certain period in which to "digest" the emotional turmoil of one traumatic experience before being exposed to another. This is best accomplished in a center where directed recreation and physical work are available, and not in the overprotected, emotionally charged atmosphere of their homes, which they meet on survivors' leave.

Those who have suffered from uncomplicated combat fatigue and who have recovered with two to three months of treatment or less are good material for retention in the service. As a rule, they should be returned to the duty they feel capable of handling. Symptoms of conversion hysteria and anxiety, not connected with startle, are bad omens. These men, with war neuroses, will eventually reach hospitals in the United States, where they will be found unresponsive to treatment until their discharge from the Naval service is assured. Their discharge need not await recovery, frequently the survey board is the therapeutic agent necessary to initiate recovery. Under governmental organization, the Veterans Administration is charged with the rehabilitation of these men.

DISCUSSION ON PAPERS BY COMMANDERS MACLEAN AND SCHWARTZ

MAJOR NORMAN LEVY: Evidently, the Aleutians, although the men see little combat except for bombing operations, present essentially the same problem of malingering as that met with in the combat personnel of the Air Forces in North Africa and Italy. My colleagues and I learned quickly that there was little practical point in attempting to differentiate neurotic reactions and malingering. The psychodynamic basis is essentially the same. The two conditions differ clinically, however. With regard to men who under the stresses of modern warfare or combat flying begin to exhibit emotional difficulties, it does not matter, from the practical point of view, whether the disabling symptoms are largely on a conscious level or are entirely on an unconscious level. The important thing is that the man is having difficulty in adjusting to the combat situation, and this condition has to be handled immediately. There is no value in distinguishing between the two. The fundamental problem, the patient's anxiety and fear in relation to the combat situation, must be attacked and therapy directed toward that rather than toward the symptoms themselves. In that way, in a large percentage of cases, one can help the combat personnel, and in many instances one can keep them continually in combat. Our experience has been exactly the same as Commander MacLean's. The men rise to whatever level is set for them, within certain limits. If one sets a relatively low level of performance by having medical officers who are overprotective and indulgent and who do not expect enough from the men in the way of self sacrifice in regard to functional symptoms, then one may have on one's hands an epidemic of these functional

symptoms. The medical officer has to be an authoritative person, who will refuse to allow men to get out of combat because of mild to moderately severe functional symptoms. That sounds, I'm sure, cruel and tough, but it is essential in the management of combat personnel who do not want to stay in combat. We had this problem with our flight surgeons. Our flight surgeons had been taught in this country that when men manifest nervous symptoms they must be grounded. In the new groups which came over, our first problem was to reorient our flight surgeons and get them to see that they had to be tough with the men and not ground them, because if they did there would be a tremendous increase in the number of men who have functional symptoms, especially conscious exaggerations of minor difficulties. As Commander MacLean found, we had to demand a good deal of self sacrifice from the men, and then they would rise to that level. If we let down the bars, they would not rise to whatever level we set for them.

LIEUT COMDR A. R. MACLEAN: Many of the things presented in my paper I have learned through the experience of other medical men who were in the service before me. They taught me the things I had to know to function as a Naval medical officer, as Major Levy, from the Mediterranean, so aptly described it, my levels had to be raised. I think that the level of psychiatry throughout the nation will have to be raised, so that the old theory of the life function of reward and punishment does not do a serious disservice to men discharged from the military service as psychoneurotic. Lifelong pensions as a reward solely for the effort made while in the Army should be considered, from our point of view, with disparagement.

DR. RALPH HAMILL, Chicago: I spent this morning at Hines Hospital, where I have spent up to six mornings a month for the past twenty-five years. As long as the Veterans Bureau is handling the problem of neurosis, there will be tremendous questions to be decided in relation to the future, if one takes into consideration what is likely to happen in the political situation, because of activity of the American Legion, for example. Any man who was discharged as neurotic at the time of World War I can now tell me any kind of story about not sleeping, his food not agreeing with him or of not being able to hold a job, and because he was discharged as neurotic in that war this condition is now service connected. Obviously, during the period of the depression money was very important, hence, one is faced with the need of considering what will happen in the next ten or fifteen years to the men in the present war whose disorders are called neuroses and are diagnosed as such. How are they going to use that diagnosis ten or fifteen years from now? Perhaps that does not apply to a great percentage of men at present, but they are the headaches of the Veterans Bureau.

ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M.B., *Presiding*

Regular Meeting, Feb. 1, 1945

The Conditioned Reflex Treatment of Alcoholism

DR. JOSEF A. KINDWALL and DR. L. H. ZIEGLER, Wauwatosa, Wis.

Experience based on 29 cases was reported, but only 3 cases were described. In 1 case, that of a woman, a strong aversion to alcohol was established, but a relapse into drinking occurred because of an extreme need of the effect of alcohol in an inadequate personality returned, with eagerness, for more conditioned reflex treatment. Barbiturates were substituted by the patient for alcohol, with a resulting toxic psychosis. Finally, she has achieved abstinence after the establishment of renewed association with Alcoholics Anonymous, Inc. (up to the time of this report) and lightened responsibilities at home.

In another case, that of a sales executive, there existed a profound underlying psychoneurosis and a pronounced deviation toward femininity, for which he unconsciously overcompensated. In his case there was an exceptionally high degree of aversion, which persisted through a series of electric shock treatments (with resultant profound confusion) given for his insomnia and tension. He was quite unable to drink liquor, though he tried in his confused phase to do so, and, though still tense and restless, he is sure that liquor will never tempt him again. In another case, that of a woman (not described in detail), the original aversion, not very strong, was further weakened by electric shock therapy, and a new series of conditioned reflex treatments failed to establish an aversion even as strong as the previous one.

The third case reported was that of a man, an executive, whose drinking had harmed him physically and who appeared dull and mentally slow on his admission to the hospital. No particular emotional problems could be found, he was a "good fellow," who had gradually become extremely alcoholic. He achieved a strong aversion to alcohol, took all the reenforcements, improved physically and, especially, mentally to a remarkable degree and has not had a relapse. He is greatly pleased with himself.

Apparently, the treatment can be helpful even if relapse does occur, patients often come back for further treatment.

The conditioned reflex—the actual aversion—is not necessarily the only valuable factor in the treatment. There are other factors, perhaps such as sacrifice, pride and emotional release, which may have an important bearing on results. The importance of follow-up observation was stressed, not only to insure adequate reenforcing treatments, but to maintain a favorable rapport between physician and patient. The authors feel that the method is a useful part of the total therapeutic armamentarium in the attack on alcoholism. The patients represented a great variety of types and of responses to the conditioned reflex treatment. More than half the patients have done well so far, the men have done better than the women.

DISCUSSION

DR. JULES H. MASSERMAN, Chicago: Dr. Kindwall requested that I devote my discussion to the possible theoretic and experimental background for his observations on alcoholism. I can do so briefly, especially since I presented a motion picture of some of my work on this problem before the society last year (in discussion on Edlin, J. V., and others: The Conditioned Aversion Treatment of Chronic Alcoholism, ARCH. NEUROL. & PSYCHIAT. **53**: 86 [Jan.] 1945). It may be recalled that the rationale of the experiments was quite simple. An animal was trained to secure food on various signals by increasingly more complicated adaptive patterns. For instance, it had to open a box, to pass barriers and, finally, to work a switch in various difficult positions. If the animal was then given alcohol, the most complex and finely tuned adaptive patterns disappeared first, leaving only the simplest feeding responses. Conversely, as the effects of the drug wore off, the more complex patterns returned, in the order

in which they were originally learned, until the full adaptive capacities of the animal were again being used After these control observations, the animal was subjected to a strong motivation conflict, such as that between hunger and fear, and acquired an experimental neurosis, characterized by evidences of anxiety, startle reactions, phobias, compulsions, severe inhibitions and "character" changes If, now, the animal was again given alcohol, these most recent and most complex behavioral expressions of internal conflicts again disappeared in part with the result that the animal reverted to similar feeding responses and so attained relief from tension and some goal satisfaction while under the influence of the drug Finally, 11 of the 21 animals which repeatedly experienced this apparent relief from neurosis under the effect of alcohol began to prefer the drug in spontaneous choices and so appeared to become alcohol addicts, significantly, too, this addiction abated as their neurosis was relieved by various other therapeutic means Perhaps it is relevant to mention an even more recent series of experiments, in which 9 animals were given alcohol before being submitted to motivational conflicts The results to date indicate that here, too, the drug acts to diminish the traumatic effects of such situations and partly protects the animals from a resultant neurosis I shall not take time to describe these experiments further, but their parallelism to the very human habit of taking "a couple of shots for a bracer" before undertaking an emotionally disturbing task deserves passing comment Finally, it may be well to mention that other experiments with the barbiturates and with morphine indicate that these drugs, too, have effects similar to those of alcohol Here, possibly, one has a clue to the reason that alcohol, the barbiturates and the opiates are the three most common forms of addiction among neurotic patients

Now, as to the relevancy of these experiments and formulations to the clinical observations of Dr Kindwall and Dr Ziegler The authors correctly point out that alcoholism is the expression of a neurotic need for a nepenthic and hypnotic drug which obliterates the poignancy of the neurotic person's perception of a world which he considers harassing and emotionally unbearable, he must, then, take alcohol to dull these perceptions and ameliorate the internal conflicts to which they give rise Significantly, too, it is not alcohol itself that is craved, rather, it is psychologic effects—a point well illustrated by the woman patient who shifted from alcohol to the barbiturates when the former was not obtainable In this connection, then, one must consider the pharmacologic action of alcohol, not merely the satisfactions of symbolic oral needs through drinking, which have perhaps been overstressed in psychoanalytic formulations Drs Kindwall and Ziegler also observed that if relief is not obtained through alcoholism internal emotional tensions may find expressions in other psychosomatic symptoms, such as the increased hypertension in 1 of their cases Again, it must be recognized that alcohol, as shown by the work of Bender and many others, has a temporary toxic or permanently destructive effect on the cerebral cortex, it is, then, perhaps even more dangerous than usual to treat alcoholic addicts with shock therapy, since there is a possibility of decorticating to an unfortunate degree some of these otherwise intelligent, capable and socially useful alcohol addicts

Lastly, one more point is perhaps worthy of discussion by the society, namely, the danger of overpublicizing this so-called conditioned reflex treatment to the point at which the public believes that there is now a new panacea for alcoholism—a fantasy which, I am sure, no psychiatrist accepts Let me quote in this connection part of a letter I received only this morning from a woman in some remote hamlet in Virginia, who writes as follows "I saw an article about your work in the local Sunday paper I have a son who has taken to drink quite a lot I have heard that there is a medicine which can be put in coffee that will put him against whiskey that maybe I can give him for his meals Please send it to me immediately" One finds it hard to smile at such a pathetic appeal, but it is up to psychiatrists to educate the public as to the neurotic nature of alcoholism and the necessity of treating it by psychiatric means, and not by pharmacologic magic

Dr Max Gitelson, Chicago I have often wondered, in connection with this method of treating alcoholism, whether the conditioning is through the drug itself or through the total situation in which the drug is given Before one goes much further in discussing specific effects produced by the giving of the drug it would seem advisable to differentiate between the conditioning to the drug and the conditioning to the total situation, including the psychiatrist, the hospital and everything else concerned with the conditioning, both positive and negative

I should like to raise the question whether it would be possible to treat some of these alcoholic patients by first conditioning them to the nauseating effect of the conditioning drug and subsequently giving them alcohol intravenously without their knowledge? Would this technic serve to differentiate the gross psychologic conditioning, which I have previously suggested may occur, from physiologic conditioning to the drug used in the treatment?

Dr Meyer Solomon, Chicago In the use of the so-called conditioned reflex treatment, is it not true that a few preliminary conditions must be present? The patient's desire to get well is a determining factor, as well as his personality makeup and his willingness to spend time and money in the treatment Is it not a fact that one must have the patient's faith and confidence that something can be done? Otherwise, the prognosis is not good Also, should not the patient's personal problems be gone into? Perhaps his ambitions will have to be brought down to a more sensible level It may be that his daily routine is too heavy, that he needs more recreational and social outlets or that a change in the kind of companions is desirable In other words, the so-called conditioned reflex treatment is just a part of the general technic, in which all kinds of psychologic factors are considered as well as the general personality of the patient

Dr Charles F Read, Elgin, Ill With regard to the reenforcing aversion treatments that are carried on at various intervals after the primary ones have been completed, has any attempt been made to conduct them with the patient under hypnosis, without the use of alcohol? Since the patients often come back for further treatment, apparently convinced that they are going to improve with another series, I wonder whether such an attempt might be tried, with some benefit, in a situation which, for them, is full of suggestions as to what may happen

Dr Josef A Kindwall, Wauwatosa, Wis I have not tried the use of hypnosis The results might be illuminating, since there is a large element of suggestion in the treatment

Dr David Slight, Chicago I should like to ask how many patients had simple vomiting, as such, and how many had nausea without the vomiting I may

have missed the description of the actual conditioning process, but I should like the authors to inform us as to what aspect of the alcohol the patients were averse Did they become averse to the smell of the liquor, to the sight of it or to the mention of the word?

DR JOSEF A KINDWALL, Wauwatosa, Wis I shall answer the last question first The conditioning was to the sight, smell and taste of alcohol Patients also displayed an aversion to the clinking of glasses, the popping of corks They would pour out smaller and smaller amounts of liquor as time went on Sometimes they would pour out a drink, say "Here's to you," and end by drinking only a little I think it is better to give the alcohol very slowly at first and let the patient smell it, put a little in his mouth and swish it around It is the taste that counts, really Later, when he begins to establish an aversion and is given a rather large drink, I suppose there is some gastric irritation connected with it But, the man whose case I described, the man who had electric shock treatments after the conditioning therapy, had a high degree of aversion to the alcohol He would claw at his mouth as though it were on fire I had another man who could not swallow the alcohol or get it down The aversion is a very real thing when it is present The first man was given a small drink, from which he vomited five minutes before I gave him the injection I delayed the injection and let him smell and taste the alcohol It is not often that one gets such a strong aversion Some people do not acquire it, and the treatment should be evaluated in these terms The patients have real nausea, not only vomiting but shuddering and all that goes with it

With regard to giving alcohol intravenously, such a method would by-pass the mechanism which is invoked in establishing the reflex To introduce the drug directly into the blood stream would immediately affect the nervous system There would be no chance for the conditioning mechanism (that is, rejection by the stomach) to take effect I suppose one would have there the same situation as in the case of the woman I mentioned, who held her nose until she got the drink down That would be a sure way of getting drunk for a person who had an oral aversion

There is no doubt in my mind that the patient's fundamental sincerity and willingness to fulfil the conditions of the treatment is of tremendous importance but that one great advantage of this form of treatment is the distaste for alcohol which it arouses in the patient In other words, I do not believe the value lies in conditioning alone Even a mild aversion is of value, because the patient has something there that he has worked hard for, has suffered for and has invested his money in I don't know exactly how to explain this in terms of reflexes, but certainly it means something If a man puts himself wholeheartedly into something of this sort, it may arouse his stubbornness in favor of abstinence, because he has worked so hard for it, and he may struggle hard to maintain it The element of sacrifice is there, too, as I mentioned in the paper The patient pays a pretty stiff price in discomfort, and I think it relieves him of his feeling of sin, perhaps that makes it easier for him I am also convinced that psychotherapy is important The conditioned reflex treatment is only a means to an end, that is, to make it easier for the patient to leave alcohol alone But the case of the woman I described illustrates that no matter how strong an aversion there is, if one needs alcohol enough one is going to take it Since we did not solve her fundamental problem, I think we were fundamentally in the dark all the time She is an extremely inadequate person, and though she is now devoting herself a great deal to Alcoholics Anonymous, she is often terribly "fed up" and unhappy She is a lazy person and says so herself She is in great danger all the time, but, after all, we have given her home a little respite, and the children ought to benefit to some extent from that

The case of the second man I described is relatively simple He is a stolid, simple person, who did not reveal any conflicts that we could get at He is married, has a very nice wife and a child He is well situated financially, has his cronies, likes to hunt and fish, but he drank just the same Well, he acquired a strong aversion, has not gone back to drinking, is delighted and is rather simple and naive about it That he has established an aversion to alcohol is the important factor He was given little psychotherapy in the ordinary sense We did not go into his problems at all, nor did he reveal any There are a great variety of cases In extreme cases the patients have deep-seated conflicts Psychotherapy, reeducation and solving of the fundamental problem would perhaps result in greater response But the relief that these persons feel when an aversion is established is amazing

The Multiple Choice Rorschach Test as a Differential Diagnostic Tool DR PHYLLIS WITTMAN, Chicago

The present study is an analysis of data obtained from use of the multiple choice form of the Rorschach test (as an individual rather than as a group technic) in the differentiation and diagnosis of psychiatric types The data on 3,150 psychiatric patients, 883 attendants, 172 professional adults and 100 teen-aged Girl Scouts were analyzed for this study

Test averages for the various groups ranged along a continuum, with the rating for the patients with hebephrenic schizophrenia at the lowest extreme and those for the professional adults at the other The results for the subjects of the other schizophrenic subtypes (exclusive of the paranoid) ranked at the bottom, near those for the hebephrenic patients, then came the averages for the patients with constitutional and affective behavior reactions, followed by those for patients with organic lesions and for the nonpsychotic, paranoid and extramural subjects, in that order

The most significant observation is the position of one of the psychotic groups (paranoid), which ranked in one of the top positions, above the group of patients who were classified as nonpsychotic. This position of the paranoid psychoses, including the condition diagnosed as paranoid schizophrenia, as well as the paranoid states, is in striking contrast to the poor level of the other schizophrenic subtypes

Observations on the present levels of adjustment of both intramural and extramural subjects and study of the social service histories of the intramural groups suggest that the type of inner adjustment evaluated by the Harrower-Erickson Rorschach test is something that might be labeled "personality integration" (Personality integration, as the term is used here, implies an intrapersonal harmony of the components making up the personality as it effects the inner adjustments of the person)

This paper presented the use of a psychologic technic as a differential diagnostic tool and concluded with an explanation of the value of diagnosis and the need for accurate and clearcut classificatory concepts from the research worker's point of view

DISCUSSION

DR V A LIEBERMAN, Elgin, Ill The clinical psychiatrist of the present day has come to rely tremendously on the exploring advantages of the original full Rorschach test Especially is this so in undertaking any intensive analysis of the personality bordering on the psychotic state The orthodox psychoanalyst, for example, has come to order a full Rorschach test in a case of incipient schizophrenia, as an internist might request a blood count Yet a test which can be given and evaluated in five to ten minutes is of greater advantage to the psychiatrist responsible for the diagnostic study of large groups of patients, such as obtain in state hospitals, with often overwhelming daily admissions of new patients The full Rorschach test, indicating in detail the analysis of a personality, is an extremely delicate instrument which can be administered only by a few highly trained persons It follows, therefore, that any effective modification of the test must be one not only adaptable to mass use but possessing scientific validity as a useful diagnostic adjunct The diagnostic utility of ratings must be dependent on the use of such ratings and signs as contributors to a clinical diagnosis, and not as a means of diagnosis themselves

The modern clinical classification of mental disorders has, unfortunately, been oriented on the descriptive level of the "label," comparisons made on the basis of similarities, with differences often overlooked or studiously avoided In this respect, the author is to be congratulated on having so succinctly delineated differences in mental reactions Her paper is based on the tests of 4,300 persons, the great majority of whom were intramural patients who could be quickly tested the very afternoon of their admission At the diagnostic staff meetings at Elgin State Hospital, this test has been of inestimable value, complementing to a significant degree whatever insight the clinician may have into the inner emotional life and constellation of the personality Conspicuous in Dr Wittman's presentation is the manner in which the schizophrenic patients stand off in statistically significant isolation, even more dramatic is the manner in which her modification differentiates the "true," or kraepelinian, dementia precox from the schizophreniform reaction types The clinician has been only too well aware of these circumstances but has often adopted the path of least diagnostic resistance The intensive research carried out by the author points to the need of a diagnostic inventory—undoubtedly many acute schizophrenic episodes might properly be included with the toxic-delirious excitements or recurrent affective states In many cases paranoid schizophrenia may belong to the category of the paranoid state, which might also include paranoid projections not necessarily organized into a system of delusional ideas —they may be bizarre and unnatural, and yet the illness may not preclude a relatively normal adaptation to tests of reality

At the Elgin State Hospital, this test procedure has found its place alongside the initial physical or mental examination

DR CHARLES F READ, Elgin, Ill In the group of patients with hebephrenic and simple dementia precox, did Dr Wittman find that there is any consistency in the grouping of the poor responses, or do they show merely a hit or miss selection, the patients perhaps exhibiting a lack of interest, attention, concentration, or whatever one pleases to call it?

DR C A NEYMANN, Chicago Dr Wittman's paper gives rise to a great deal of speculation in regard to the Rorschach test This test produces personal reactions from the patient, and its interpretation may also be subjective, though its advocates claim the opposite In view of this, I congratulate Dr Wittman on her paper, which allows a more objective interpretation A question as to two points would seem to be proper Can Dr Wittman give us some information about the validity and the reliability of this new test?

DR PHYLLIS WITTMAN, Chicago There may be differences between these two types of schizophrenia and all other forms One of the things my associates and I plan to do is to construct differential profiles showing on what particular cards and in what way the subjects with "process," or "true," schizophrenia differ from the subjects with schizophreniform and with other types of psychotic behavior reactions The differential profile will indicate the characteristic response to each card for each group of subjects We think we shall be able to find profiles that may distinguish hebephrenic and simple schizophrenia from the other types Therefore I think that I can say "yes" to the question whether there were certain categories of responses which differentiated the process schizophrenia from the other types

In answer to Dr Neymann's questions The validity of the scale is questionable That is, the test is still a research tool I myself give a different interpretation to the meaning of the results than that of Dr Harrower-Erickson, which is an evaluation of emotional adjustment, since this does not fit the results which we obtained The quality of personality integration is a better indication of what the test shows according to our results

The reliability of the test is much less open to question than its validity We have used the test on the same patient both before and after therapy and at other times as well We have also used other cards, including Behn's and Harrower-Erickson's cards, as well as the original tests, and our results with the multiple choice scale are very similar to those with these forms of the test

In answer to Dr Slight's question First, I did not emphasize that the modified multiple choice Rorschach test in no way takes the place, or can be considered the equal, of the original Rorschach scale It is simply another tool, one that is more objective than the latter, and can be used by one less skilled in the Rorschach technic, or even by one not skilled at all It can be given to a large number of patients in a relatively short period Many patients who are uninterested and have to be urged to cooperate in many of our psychologic tests will respond rather well to the Harrower-Erickson Rorschach test The purpose for which this particular scale was developed was to secure a test that was not so time consuming and not so difficult to evaluate as the Rorschach test, one which could be used as a weeding-out device for selectees and which could be given in a relatively short time and to a large group of persons It was primarily developed for differentiating draftees who are too disturbed psychologically to be fit subjects for military training We have adapted it to use with state hospital patients by using it as an individual rather than as a group technic If one is familiar with the Rorschach test, one will notice that each choice is associated with a certain type of response which gets a similar weight on all the Rorschach cards —for example, an organized whole response, a purely color response or a definite form response

The results for the psychopathic personalities disturbed me I have been able to explain to my own satisfaction the other results we obtained I do not have any explanation for those for the psychopathic personality We found a number of such patients

who did very poorly Then there were a number, although not quite so many, who did relatively well I don't know why that should be I wonder, however, whether it might not be related to the indefiniteness and looseness of the diagnostic concept "psychopathic personality" The term seems to be a catch-all for those states which do not seem to fit into any other classification

Education, Reeducation and Psychotherapy DR JACOB W KLAPMAN, Chicago

Mental disorders may arise from repressions and distortions in the more somatically linked affect There is also reason to believe that the affect and drive may show some constitutional weakness, giving rise in their extreme forms to what is often alluded to as "process schizophrenia" But, ordinarily, the breakdown in personality under apparently mild stress is importantly contributed to by the faulty conditioning of the apperceptive apparatus This, of course, means faulty education

As a result of acquisition and perception of facts, characteristic patterns of adjustment in the form of attitudes are brought into being It is the attitude which carries the affective charge It is, in fact, the bridge between the intellectual and the affective-instinctual life of the organism Since attitudes are founded on experience, facts and supposed facts, the importance of the latter becomes apparent

The perception and well balanced apperception and interpretation of facts in one's complicated environment, so that realistic and adaptative attitudes and adjustments can be made, are by no means a foregone conclusion and indicate the future tasks and present defects in the present educational institutions The result is that, whereas individuation proceeds, there is not a corresponding growth of the self The result might be described as "tubular intellect"

For the correction of these elements of maladjustment the reformation of basic attitudes is necessary Unquestionably, there are mental disorders arising principally from distortions in the more somatically linked affect and instinctual drive But even these are maintained through the sensorium and intellect, whose apperception of reality, originally thus conditioned, constantly maintains the affective disorder In consequence, the person further exerts a selective action on his perceptions of reality, producing a fixed system of interaction

In psychotherapy it becomes necessary to attempt to break this vicious circle The analyst and psychotherapeutist allow, by their permissive attitude, the liberation or partial liberation of distorted affects Through the transference and suggestions of the therapeutist, it follows that the therapy is accompanied with some enlargement of consciousness and intellect There is still the possibility, nevertheless, that much of the drive thus liberated, much of the affective valence thus rendered available, may be incorrectly combined This is the meaning of the transference neurosis Chances for combinations which are socially well adapted and personally gratifying, too, are increased by placing at the patient's disposal a greater range of facts, attitudes and concepts Furthermore, if the properties of these facts and attitudes are shown in their context and their relationships to the whole welter are carefully delineated, the choice is greater and more accurate Obviously, this was the original intention of education and must again be made the aim of reeducation.

In individual psychotherapy, what reeducation takes place occurs largely through the transference The patient accepts this orientation mostly on faith, because the therapeutist says so He is, therefore, dependent on his therapeutist, and it may still be questioned whether analysis of the transference neurosis may not still leave much affective valence unsatisfied Indeed, one often sees clinically schizophrenic patients who have recovered from the psychotic episode exhibiting no psychotic manifestations except what may be called "free floating anxiety"

It would seem, therefore, that the sensory-apperceptive-intellectual part of the personality must be equally reordered for optimum psychotherapeutic results

DISCUSSION

DR MAX GITELSON, Chicago This discussion is somewhat handicapped by the fact that I have not read the paper, which is greatly condensed and presents a rich material However, I think there is a considerable amount of validity in Dr Klapman's description of the problems involved in psychotherapy I obtained the impression, in listening to the paper, that the task of the psychotherapeutist is to help the patient in testing reality, that is, to help the patient reenforce and "revisualize," if I may use the term, the emotions involved in his illness in juxtaposition to the symbols and meanings related to these emotions This, of necessity, in certain types of psychotherapy, perhaps most characteristically in analytic types, means the use of the intellectual powers of the patient However, one cannot depend exclusively and finally on the intellectual powers There is one absolute exception which will demonstrate my thesis that one is not utterly dependent on the powers of the intellect in treatment The evidence lies in the fact that with children, especially extremely young children, in whom the intellectual capacity is formative, so to speak, it is still possible to do reconstructive psychotherapy with a minimum of dependence on symbols and with maximum reference to meaningful attitudes, postures and actions of the psychotherapeutist vis-a-vis the immediate postural responses, mimicry and general bodily activity of the child

As a specific example, at present in the clinic at Michael Reese Hospital, my associates and I are treating a deaf mute, 4 years old, who is making remarkable therapeutic progress by means of communication which is symbolically understandable, though consisting only of postural attitudes and physical activity expressive of the child's interpersonal attitudes and capacity for relationship The inability of the child to communicate and to symbolize by the usual verbal means has been no barrier to treatment

DR C A NEYMANN, Chicago It has been my experience in treating patients with neuroses that the most intellectual patients do not necessarily make the most rapid recovery Frequently, the dull and backward make a quicker recovery This certainly has been true of my latest experiences at the Veterans Rehabilitation Center The woman who exhibited a paranoid state in connection with her teeth, because she believed the dentist had used the wrong teeth in making a denture, certainly was stupid, if not feebleminded Such patients generally are not classified as paranoid but, rather, as feebleminded with paranoid trends Probably because of the highly selective symbolism and her lack of intellectuality, she made an unusually quick recovery In other words, there was a decided interrelation between her stupidity and her acceptance of a simple factual explanation

DR JACOB W KLAPMAN, Chicago What the discussants have said is much to the point There are undoubtedly many patients whose personality disorders can be adequately treated by the means mentioned but

I am impressed by the fact that there are patients who have a very poor object relationship and are interested in nothing, and one scarcely has a handle to their personalities They have not developed any real interest in the world The emotional life has, therefore, found few points of attachment, with a tendency to curl up on itself in a condition of narcissism I have speculated that the antidote may be an attempt to reeducate with a view to draw out the affect and anchor it securely to objects in the environment That is the biologic significance of education, the task of reeducation and a prime consideration in psychotherapy

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

BYRON STOOKEY, M D, *President, New York Neurological Society, Presiding*

Joint Meeting, Jan 9 1945

Studies on Flying Personnel with Operational Fatigue. Studies on Dextrose Tolerance and Electroencephalographic Patterns

MAJOR BENJAMIN H BALSER, Medical Corps, Army of the United States, and DR BERNARD L PACELLA

One hundred members of the United States Army Air Corps with a disturbance diagnosed as operational fatigue were studied from the point of view of their electroencephalograms and dextrose tolerance curves Thirty-eight per cent of these patients responded to the ingestion of dextrose with a "flat" curve in that the blood sugar did not rise significantly above the initial value and hypoglycemic levels developed rapidly Eight of the patients whose oral dextrose tolerance curves were "flat" were studied by means of the intravenous administration of dextrose and exhibited sugar tolerance curves within normal range Since the dextrose tolerance curves obtained with intravenous administration revealed no abnormalities, it is suggested that the "flat" curves after oral ingestion may not be indicative of a disturbance in the metabolism of carbohydrates but may be related to some disturbance in gastrointestinal activity whereby the absorption of dextrose is decreased

Abnormal or borderline electroencephalographic records were obtained from 34 per cent of the patients, of which 20 per cent were abnormal in the resting state prior to hyperventilation No significant correlation between the electroencephalographic abnormalities and the dextrose tolerance curves was apparent

DISCUSSION

DR RICHARD BRICKNER I wish Dr Pacella would say a word about a matter which frequently puzzles me in reports on men like these, who apparently have definite somatogenic disturbances, in this case fatigue, which would seem to be ample cause for the symptoms Usually it is asserted that there is a psychogenic disturbance as well, but often the proof of this appears to be unsatisfactory For example, some of the men in the South Pacific who had malaria, dysentery and extremely fatiguing experiences are spoken of as having psychogenic disturbances Discussion on this point would be welcome

DR LAWRENCE S KUBIE I wonder whether it is wise to use the concept of "operational fatigue" at all in a scientific discussion of this problem There can be no question that the term has considerable practical value in the military setting, for to label an illness as a neurosis has certain automatic results on such matters as a man's flying status, his earnings and his veteran's rights It was to avoid this that the Army devised the term "operational fatigue" It might equally well be called anything else Therefore when I heard Dr Pacella say that this condition is due half to emotion and half to fatigue, I realized the danger of accepting this scientifically meaningless term as a conceptual basis for scientific investigation of the problem This can lead only to confusion

DR MARGARET A KENNARD I should like to ask Dr Pacella whether he has made quantitative determinations of the percentage of alpha activity The reason I ask is that my colleagues and I have made determinations on patients with delirium tremens who show many such symptoms—sleeplessness, anorexia, extreme "jitteriness" and hyperactive knee jerks, and these patients have a high percentage of fast activity and far less alpha activity than do normal subjects We also have some indication that patients with other disturbances associated with intense anxiety who show such symptoms as tremor and increased reflexes have an increase in fast, 20 to 30 per second, activity

I should also like to ask whether the electroencephalograms were obtained before, during and after intravenous administration of dextrose If I remember rightly, in Feinsinger's work on the electroencephalograms of a normal group, there was a much higher percentage of abnormality in the electroencephalogram of the subject when the glucose levels were low than after the intravenous administration of dextrose

DR HAROLD G WOLFF Will Dr Pacella discuss for us the implications of his work?

DR BERNARD L PACELLA The question which Dr Brickner and Dr Kubie raised with regard to the scientific validity of delimiting a clinical syndrome designated as operational fatigue is an important one I do not consider myself fully qualified to judge the validity of such a classification because of my limited clinical contact with the personnel of the Air Forces I might, however, refer to the observations of medical officers in the Army Air Forces that this syndrome, which they describe as "operational fatigue," appears in a man who has been flying at least several hundred hours and after he has been on a number of combat missions Hastings differentiates between the men who "break" early and the men who "break" late He states that the former generally exhibit anxiety features before they have been involved in much combat activity, and he finds that they usually have shown neurotic traits earlier in life This group is usually unfit for further combat flying However, the men who break late after they have been through a number of harrowing and fatiguing experiences, are classified as having operational fatigue They always seem to have a depression, in some cases rather severe They practically always have a gastrointestinal disturbance, in addition to the symptoms I have already mentioned The diagnosis of operational fatigue is not made unless, so far as can be determined, these men have shown fairly stable personalities all through life, in contrast to the men who break early, in whom instabilities of personality have prevailed previously

I am grateful to Dr Kennard for the questions which she has raised First, the question whether dextrose was administered before the electroencephalographic recording It was impossible for us to carry out this

procedure because of the necessity of making electroencephalographic studies on large groups of patients in very short periods We realize that there may be a source of error here, but it is doubtful whether it would significantly alter our results

As to the question about the percentage of alpha activity in our records We did not carry out quantitative studies on this point With respect to the effects of anxiety or tension on the alpha waves, I think there may be differences in the effect between severe anxiety, as observed in the neurotic patient, and ordinary tension as it appears in normal persons or in other subjects who come into the electroencephalograph room for the first time In the last-mentioned subjects one usually sees a diminution in the alpha activity, whereas in patients suffering from severe anxiety we have often observed a high amplitude, high incidence alpha rhythm This, in fact, was illustrated in case 2, in which I pointed out the high frequency of alpha activity over the occiput

Dr Wolff inquired about the implications of our results We are presenting them merely as observations at present, and we are hesitant to proceed further with theoretic considerations as to the meaning of these observations The report is a preliminary one, and we have avoided much discussion of the possible implications One or two points were brought out First, there is a possibility that in some of these cases the disturbance might be related to a concussion state However, this is largely conjectural Some of the electroencephalographic records have resembled strikingly the patterns observed with concussion syndromes, but there, again, such tracings are essentially nonspecific and cannot be offered as valid evidence of such a condition If we were able to study these patients over a longer period, we should have more evidence along these lines

Second, studies of the blood sugar suggest that the explanation may be a low rate of absorption of sugar from the gastrointestinal tract, although other factors may play a role in the production of the "flat" oral sugar curves

Camptocormia A Functional Condition of the Back in Neurotic Soldiers

LIEUT COL S A SANDLER, Medical Corps, Army of the United States

Camptocormia is a hysterical phenomenon seen during wartime in certain neurotically ill soldiers

1 It is manifested by pain in the lumbar area and by a bent trunk The condition may or may not be precipitated by trauma and is of functional origin

2 In cases of this syndrome there is not only adoration of but a suppressed ambivalent irritability and hostility toward the father There is a strong overidentification with the father, who also generally had symptoms referable to the back In the only 3 cases in our series in which the mother had serious trouble with her back it is remarkable that the fathers were either killed or died before the patient was 5 years of age, therefore the mother not only fulfilled her own part but assumed the masculine role of the absent father This gives rise to speculation regarding the effect of the death or absence of the father on the psychosexual development of these men

3 The onset of this back-bending phenomenon is concomitant with or preceded by impotentia, which I believe is rather general in camptocormia and is probably indicative of the soldier's latent homosexuality and castration anxiety

4 The ambivalent feeling toward the father reflects itself toward authority in the military situation, with resulting projection of resentment on commissioned and noncommissioned officers The military situation is the source of constant threat and danger to the ego, which continually strives for its safety and protection When the pressure becomes too great, the ego wilts, and symptoms of camptocormia develop We have observed that when these soldiers find asylum from the rigors and dangers of war by admission to an Army hospital, with knowledge of subsequent discharge from the service, this is sufficient to produce disappearance of symptoms

5 This condition of camptocormia not only is a phenomenon in military life but is occasionally seen in civilian life after industrial and other types of accidents, but it is frequently unrecognized

This paper was published in full in the July 1944 issue of *War Medicine*, page 36

DISCUSSION

DR L D FRIEDMAN It is interesting to hear Colonel Sandler speak of this condition, for during World War I there were a number of cases I saw some of them, I also have seen some cases in which the disturbance resulted from an industrial accident As is generally known, the term camptocormia was coined by Babinski after the last war, he was fond of Greek derivations In the same volume in which he described camptocormia, he described pithiatism—his term for suggestion neurosis He also is responsible for the term adiadokokinesis

Bent back is a nonorganic syndrome which is stubborn to therapy and persists for a long period

I should like, without disparaging the dynamics suggested by Colonel Sandler, to bring into relationship with this syndrome the case of a child with encephalitis whom I observed at Bellevue Hospital (perhaps Dr Denker remembers the boy) As a result of this illness not only did typical paralysis agitans develop, but he began to stoop forward more and more, so that he became almost a quadruped Thinking in terms of primitive patterns of activity, one would say he had made a phylogenetic recession to the quadruped phase of locomotion One sees other release phenomena in the wake of encephalitis—for example, the rhythmic protrusion of the tongue, as exemplified by the panting dog, and periodic fishlike opening of the mouth It may be fair, therefore, to state, in the sense of Wilson, that these patients with bent back make a similar phylogenetic recession to the level of the basal ganglia It would be interesting to follow these patients for a time and see whether one can demonstrate such a mechanism

DR ISRAEL STRAUSS I am much interested in Colonel Sandler's paper It is difficult to explain attitudes such as this on a functional basis Colonel Sandler's expression of the dynamics is satisfying It is satisfactory to persons who are familiar with the freudian concept By those who are not, who do not understand them or who insist that one must look for something else these patients will often be regarded as malingerers Personally, I hesitate to make a diagnosis of malingering in civilian life I have not dealt with the soldier, but I have always felt that most malingerers have a psychopathic personality, even though it appears to the casual observer that the malingering is motivated by self interest I mention this because Colonel Sandler says these patients became erect the minute discharge was in view As Dr Friedman said, it would be interesting to follow these men The difficulty with much of the work presented at present by Army officers is that there is little follow-up observation What I say with regard to Colonel Sandler's paper applies also to the previous paper It is the follow-up study which will

tell whether the ideas expressed in the paper have validity and will offer the explanation However, there is one thing one must be careful about In the first case presented by Colonel Sandler there was a history which would generally be interpreted as indicating a protruded intervertebral disk, the result of repeated trauma to the back caused by the lifting of excessive weights As a matter of fact, only recently a United States soldier who was discharged was brought to me because he had recurrent backache He had been hospitalized frequently, and he was bent down and could not stand up When he received his discharge, he stood up However, I felt there was something more than a psychologic situation, and he was sent to one of the local hospitals, where the intern told his chief there were no physical indications in the case, that the man's trouble was in his head, not in his back The soldier was discharged I met the attending physician, who is an excellent surgeon, and I said, "Too bad you were listening to the resident, suppose you go in with the knife and see whether it is in the head or in the back" He found a large intervertebral disk protruding, and the man is now cured of the camptocormia This is not told in a derogatory way, it is said to illustrate the need of being on guard, and no one knows that better than my friend Colonel Sandler I mention this only in regard to the first case, in the others the history did not lead one to suspect a protruding intervertebral disk

DR BYRON STOOKEY I think that is why Colonel Sandler put the case on record, I believe it is the only one in which the patient escaped the Army without being operated on!

DR IRVING J SANDS I should like to ask Colonel Sandler whether any psychometric tests were made on these patients, and, if there were, what were the intellectual levels?

My experience in World War I leads me to believe that this condition is rare, among some 3,000 patients in ward 55 of General Hospital No 1, and among the many patients that I have seen at the outpatient department of United States Veterans Hospital No 81 over a period of eight years, I do not recall a single case of the disorder I am, however, much interested in the intellectual level of Dr Sandler's patients, as I believe it will bear a definite relation to the manifestations of this conversion hysteria

DR RENÉ A SPITZ In these cases there are two satisfactions which the patient gets, or, rather, two aims which he is able to achieve with the help of his bent back 1 In military service these men, who are extremely ambivalent and unctuous when examined by their officers, achieve through their bodily position the possibility of avoiding standing at attention, in other terms, their bodily position is disrespectful to their officers because they do not stand at attention, but at the same time they bow respectfully 2 In civilian life these men, who seem to show a previous history of sickness, are mostly impotent This bodily position makes intercourse impossible and serves to justify their avoidance of it

DR EDWIN G ZABRISKIE I came in at the end of Colonel Sandler's paper, so I shall speak on only two points One is that I never saw a case of camptocormia in France or in this country, my experience being the same as Dr Sands in this respect I have heard of the condition, but it was never my fortune to run into a case Second, in the Army, we recognized only two types of malingering in France, one was the self infliction of a wound, and the other was straggling on the way to the front The French recognized this and dealt with it strictly, by shooting the men, as a result, the practice ceased to be a problem In the United States Army they did not go quite that far

DR BYRON STOOKEY May I ask Dr Strauss and Dr Friedman, who have had a vast experience, how many cases they have encountered in their civilian practice I ask because I have not encountered any, nor do I remember having seen any in my service in the last war in the British army, in 1915 and 1916, or in the United States Army, in 1917, 1918 and 1919 I should like to know whether Dr Strauss and Dr Friedman have encountered any cases in civilian practice

DR ISRAEL STRAUSS I have not

DR E B FRIEDMAN I have seen 2 cases, and I think Dr Brock has seen 1 case, as a result of industrial accidents

DR BYRON STOOKEY The practices of Dr Strauss and Dr Friedman represent an enormous clinical experience, so it must be a rare condition

DR LAWRENCE S KUBIE Any dramatic symptomatic disturbance such as this exerts a strong suggestive influence on other men, particularly when men are kept together over a long period or the men are of low mentality and show considerable passive suggestibility This bears out the dynamics which Colonel Sandler has described I should not be at all surprised if such cases occur in sudden outbreaks in groups of men, among whom group contagion is active In certain of the cases described by Colonel Sandler, the role of group suggestion was particularly clear, as in that of the man who came in with headaches but who ended with severe camptocormia

I should like to make one other point, a chronic organic lesion of the lower part of the back, such as a protruded disk, will gradually become interwoven with all the emotional disturbances latent in the personality In such a situation it is difficult to know which attacks are hysterical and which are organic That camptocormia should develop subsequent to a long history of pain in the lower part of the back is wholly understandable

DR RENATO ALMANSI I had the opportunity of observing a case of camptocormia in a Negro soldier several years ago He was a man of low intelligence and was very ignorant, and there was a definite reason in his surroundings for the development of his symptoms, inasmuch as he was dissatisfied with his superiors and officers In that particular case I was stern with the patient, not because I assumed he was a malingerer (I was perfectly satisfied that he was not), but because I thought that his condition would be benefited by a firm attitude Thus, by taking away from him all the satisfactions that his condition had given, I was able to correct his camptocormia in a few days

Colonel Sandler mentioned that the condition of his patients cleared up as soon as they were discharged from the hospital I wonder whether a firm attitude toward them would not have achieved the same result

DR BYRON STOOKEY May I ask Colonel Sandler how frequently this condition is encountered in Army camps of comparable size and whether he is aware of any Army statistics which would be of interest I heard him refer to 2 other cases, the assumption being that, so far as he knows, no other cases have been reported

DR ISRAEL STRAUSS I should like Colonel Sandler to state how many men with this disorder were in camp at one time and what their contact was with each other I ask that in connection with Dr Kubie's question

LIEUT COL S A SANDLER I wish to thank the discussers for being so charitable and for not trauma-

tizing me too much I shouldn't want to go back to camp with camptocormia!

Dr Strauss's contention that it is possible for these patients to have a lesion of the cord is quite correct, except in the case of the soldier he discussed—that man had no radicular signs or any localized pain Also, it is to be noted that he had four attacks in civilian life, previous to induction into the Army and he specifically pointed out that at the onset of three attacks he was with some one to whom he had a strong emotional attachment, once his father, once his wife and the third time his best friend

Dr Strauss's contention that suggestion has considerable influence in this condition is correct, because of its hysterical character, suggestibility, as far as other soldiers are concerned, was indeed a difficult problem

I watched these patients for a considerable period I was "between the Devil and the deep sea" As a staff officer (I happen to be not only a medical officer but a staff officer) part of my duty is maintaining and enhancing the morale of the training center, and therefore on many problems I see eye to eye with the line officers We wanted no man discharged from the service unless he was really ill, on the other hand, there was the problem of how to control the possibility of mass suggestion It is true that when these men started coming in, most of them seemed to be from the same companies, and there is no question but that there was an element of suggestion

In reply to Dr Stookey, may I say there has been little published on this condition? The largest series consisted of but 2 cases, reported by Lieut Col Percy G Hamlin (Camptocormia, The Hysterical Soldier's Bent Back, *Mil Surgeon* **92** 295-300 [March] 1943) However, when, at a conference of neuropsychiatrists in a certain camp a few hours ago, I said I was coming here to present these cases of camptocormia, they all agreed that they had seen a number of such cases One medical officer facetiously remarked "If you need cases to present, I can let you have about 30 from my ward" Although I have presented 19 cases, I have seen almost twice that number

I learned something here tonight from Dr Friedman (as I usually do) Only today one of the medical officers in another camp, referring to camptocormia, stated "While your men with camptocormia are all bent forward, I have a man in the opisthotonos position How do you account for that?" I replied that in the camp with which I was associated they all seemed to follow the same pattern, however, I think Dr Friedman's suggestion that the condition is an encephalitic manifestation might be correct

Dr Sand's question is a good one He is correct in his assumption that these men had low intelligence quotients Their average period of schooling is about seven years in grade school, as compared with a group of somnambulists which I reported on at the meeting of the American Psychiatric Association last spring, whose average educational level was about three years of high school The proportion of Negro soldiers was much greater than that of white soldiers (I think my reply to Dr Sands also answers Dr Kubie)

One of the discussers asks whether firmness would have been helpful The answer is "No!" Neither firmness nor kindness seems to have any effect so far as cure is concerned There is a kind and understanding psychiatric chief in the station hospital, and I must reiterate that no amount of kindness seemed to obtain results, unless that kindness was associated with a discharge from the service! Treating these soldiers with firmness and pointing out to them that they were expected to remain in the Army only seemed to complicate matters, but, as previously noted, kindness or firmness, if associated with a certificate of disability discharge, appeared to be the answer

Distant Secondary Circulatory and Vasomotor Reactions to Accidental Electric Shock

DR GEORGE H HYSLOP

Alexander (*M Clin North America* **22** 663, 1938) stated that 25 milliamperes or more may produce permanent damage to nerve tissues and blood vessels

One may define direct primary effects as limited to tissues traversed by the current Indirect, or secondary, effects are those which occur in other tissues as a result of a reaction originating in tissues traversed and directly affected by the current

Weeks and Alexander (*J Indust Hyg & Toxicol* **21** 517, 1939) demonstrated that the current chooses the shortest path from contact to contact without deflection by anatomic landmarks (thus indicating that the body acts as a "structureless gel") They also demonstrated that in tissues adjacent to, but at a distance from, the current main path the effective current conducted rapidly decreases, that is, there is practically no diffusion of the current at a distance from its main path As for blood vessels, it has been shown by Echlin (ARCH NEUROL & PSYCHIAT **47** 77 [Jan] 1942) that when the current traverses arteries there is an initial constriction followed by a period of dilatation, which may be extreme and prolonged and cause secondary hemolysis of the blood in the veins These reactions are limited to vessels traversed by the current

Alexander (ARCH NEUROL & PSYCHIAT **47** 179 [Jan] 1942) stated "In hand to hand contacts cerebral changes are not due directly to the current but are caused by the prolonged circulatory disturbances produced by passage of the current through the heart and the endings of the vagus nerve"

Instances are known in which no loss of consciousness occurred and the current pathway did not reach the brain, but within a few minutes to two or three days the victim manifested signs of focal reaction in the brain As yet no satisfactory explanation has been offered for such delayed and distant tissue reactions

Scheinker (ARCH NEUROL & PSYCHIAT **52** 43 [July] 1944) presents certain conclusions which are perhaps germane Scheinker's paper is concerned chiefly with the effect of mechanical trauma on blood vessels However, he points out that profound circulatory disturbances may be seen in regions remote from the direct influence of the irritant stimulus, thus indicating that the stimulus is probably transmitted over a neurovascular network to the distant subdivision of the vascular tree If there is circulatory stasis, there is local accumulation of carbon dioxide, which is a particularly active vasodilator If it continues to accumulate, there are further vascular dilatation and increased permeability of the vessel wall, with actual degeneration and necrosis of the vessel walls if the alterations are sufficiently severe Thus, the essential vascular factor for involvement of surrounding tissues is the increased permeability of the vessel wall

If current traverses the cervical sympathetic fibers, it is not unlikely that the vessels of the brain may be affected When the splanchnic and abdominal sympathetic ganglia are violently stimulated, with possible spread of the impulses to the cervical sympathetic fibers, reaction of the cerebral vessels could occur There

might be immediate transient symptoms of focal nature if the effects on the vessels of the brain were limited to brief spasm If the vessel wall were to suffer structural damage, with impairment of permeability, effects on surrounding brain tissue might be delayed, so that local clinical symptoms would not be evident for even a few days

DISCUSSION

DR WILLIAM A GEOHEGAN (by invitation) Dr Hyslop has presented an interesting possible explanation of some of the indirect and delayed reactions to electric shock As he has pointed out, Weeks and Alexander showed that electrically the body behaves as a structureless gel and that therefore most of the current passes directly between the points of contact and the current passing outside this path is relatively small It might be noted that the apparatus they used permitted measurements of current only as small as about one twentieth of the current at the point of maximum current density in shocks of lethal magnitude, in view of the fact that in certain circumstances extremely large shocks may be tolerated without causing ventricular fibrillation, it is quite possible that in some cases there may be cerebral damage due to the current itself However, it is clear that in a considerable number of cases, as Dr Hyslop has pointed out, there are cerebral effects that cannot be explained on the basis of the passage of the electric current itself It has been generally considered, as he has pointed out, that these changes are related to circulatory factors, but no one has ever described the exact nature of these alterations except to note the results of stimulation of the vagus nerve Because of the importance of the sympathetic chain in the control of cerebral vessels and its position in the path of greatest current density in arm to arm shocks, it is reasonable to assume that it might have considerable influence on the vessels in cases of electric shock It is not necessary to assume any permanent tissue damage in the sympathetic chain As Speidel has shown in moving pictures of living tissue, with even slight electric shocks it is possible to get retraction of nerve endings and subsequent growth, so that even a small shock may change the pattern of the sympathetic response If one attempts to explain the effect on the brain entirely in terms of the effect on the sympathetic nervous system and, further, on the impulses in the cervical portion of the sympathetic chain, the exact pattern is hard to visualize If one were to assume that the change is due to cessation or diminution of impulses in the cervical sympathetic chain, one would have to explain why the same condition does not arise in cases of bilateral stellectomy If one were to assume that it is due to an increase in activity, one would have to explain why the same situation does not arise with irritative lesions of the cervical sympathetic trunk Therefore it does seem hard to explain the picture on the basis of altered impulses in the cervical sympathetic chain itself However, it is reasonable to assume that the altered function in the sympathetic trunk may be contributory in producing vascular changes, which, added to those in the systemic circulation, might cause such effects as those described Animal experimentation to determine the exact nature of this altered function might be undertaken, some of the possibilities might be fairly easily investigated, while others might be difficult For example, one might record electrically from the cervical sympathetic trunk, or one might study the vessels in the brain before and after shock, both with and without previous stellectomy These experiments would give evidence of a positive nature in some cases and of a negative nature in others, because performing the stellectomy would merely remove the effect of the cervical sympathetic chain and one could not then study directly the effect of inhibition of the cervical sympathetic chain as compared with the effect of leaving it intact This might be done in a sufficiently large series by comparing results with observations on normal animals I believe that investigation of this problem by means of animal experimentation might lead to interesting observations on the action of the sympathetic nervous system in such cases as Dr Hyslop has described

DR BERNARD L PACELLA I should be interested in knowing Dr Hyslop's opinion regarding the possible distant effects of electric shock therapy on the central nervous system, inasmuch as controversial opinions are expressed in the literature However, it may be noted that in patients who have been accidentally "shocked" the voltage required is usually greater, and the time of passage of the current through the body is generally longer, than in therapeutically "shocked" patients

My associates and I have not observed in any case clinical evidence of focal cerebral lesions, yet the electrodes are always put directly on the head, so that the current flows through many of the important structures of the brain We do find electroencephalographic evidence of some disturbance weeks after patients have received electric shock therapy, but we have not yet observed electroencephalographic evidence of focal damage

DR GEORGE H HYSLOP One does not like to lay an egg without sitting on it long enough for it to hatch I realize perfectly well that this hypothesis has as yet no experimental demonstration I laid this egg hoping that with the passage of time and the eventual availability of experimental animals and all the other requisites, physiologic corroboration or refutation of this hypothesis could be made In addition to the particular line of animal experimentation mentioned by Dr Geohegan, there would be another, namely, that the animals subject to the experimentation should have the current travel from hindlimb to hindlimb or directly through the trunk, and presumably directly affecting the thoracic and abdominal sympathetic ganglia I presented the subject in the hope that it might intrigue at least those who have had to deal with the clinical effects of accidental electric injuries

Apropos of Dr Pacella's discussions, there is a fairly abundant literature on the histologic effects of electric shock on the brain These effects are identical with, and less in degree than, those associated with metrazol shock, and most of the damage is not due to the burning effects of the electric current There is abundant evidence, translated from the animal and corroborated by autopsy on persons who have died, sometimes of cardiac but not of cerebral cause, that electric shock produces diffuse damage which from a clinical standpoint may be only transient

As to the final clinical reactions, some have been bandied about by word of mouth but are not in the literature One hears of patients who, after a certain period, lose the higher intellectual abilities and are disqualified from certain types of occupation It is a well recognized fact that some of the electroencephalographic effects may persist for months after electric shock treatment is over—evidence that this treatment is not to be taken lightly, any more than a demonstrable cerebral reaction to infection or injury can be passed over lightly

CHICAGO NEUROLOGICAL SOCIETY

RALPH HAMILL, M D, *President, in the Chair*

Regular Meeting, Jan 9, 1945

Arnold-Chiari Deformity in an Adult Without Obvious Cause

DR PAUL C BUCY and DR BEN W LICHTENSTEIN

The term "Arnold-Chiari deformity" is generally used to designate a specific modification in the configuration and location of the hindbrain It is usually found in association with spina bifida or platybasia Formerly looked on as a malformation, it is now generally conceded to be a deformity resulting from abnormal forces exerted within the craniospinal cavity Its occurrence with spina bifida is believed to be due to abnormal fixation of the spinal cord, its roots and meninges Its occurrence without obvious cause is unusual, and its early recognition is of practical importance, for great improvement in the neurologic picture follows surgical decompression of the craniospinal junction

The authors report the case of an American Negro woman aged 40 who had had paresis of the lower extremities and the right upper extremity for approximately one and one-half years prior to surgical exploration The weakness in the extremities was associated with sensory disturbances in her right hand and atrophy of the right side of her tongue For many months she had been believed to be suffering from a vascular lesion in the medulla oblongata Spinal puncture revealed complete spinal block Suboccipital exploration revealed a typical Arnold-Chiari deformity, the medulla oblongata and the tonsils of the cerebellum being displaced into the upper cervical portion of the spinal canal The right hypoglossal and spinal accessory nerves were found to be elongated and tense After decompression the patient made an excellent recovery

No evidence of spina bifida or platybasia was noted Similar cases were reported by Adams, Schatzki and Scoville and by Aring The clinical picture usually becomes fully developed about two years after the onset of symptoms The symptoms fall into four groups (1) those resulting from increased intracranial pressure, such as choked disks and headache, (2) those indicative of involvement of the lower cranial nerves, (3) pyramidal signs and sensory disturbances resulting from compression of the brain stem or the spinal cord, and (4) cerebellar signs

DISCUSSION

DR PETER BASSOE In the 1 case without spina bifida in which autopsy was performed, I should like to ask whether the lower part of the spinal cord might have been fixed early in life by some other process, such as meningitis

DR GEORGE B HASSIN I should like to ask Dr Bucy whether hydrocephalus does not usually occur with spina bifida as a manifestation of general hydrops of the brain, including the brain stem, and whether at the time of operation such signs were present I should also like to ask Dr Lichtenstein whether in cases of curvature of the spine, such as kyphosis or angular fractures, the spinal cord is stretched Why are signs of hydrocephalus, which in cases of spina bifida are supposed to be due to pulling or stretching of the spinal cord, absent in the instances mentioned in which the spinal cord greatly deviates in following the spinal deformity?

DR PAUL C BUCY Dr Hassin is correct, the Arnold-Chiari deformity is commonly associated with hydrocephalus It is, in fact, one of the common causes of hydrocephalus in children who have a meningomyelocele In the present case no ventricular study was made prior to operation, and at the time of operation edema of the tissues was not observed We therefore have no direct evidence as to the presence or absence of ventricular dilatation

DR BEN W LICHTENSTEIN In answer to Dr Bassoe, I wish to state that many cases have been described in which the Arnold-Chiari deformity was found in adults at autopsy This was generally in association with platybasia In Aring's case no spina bifida was noted

In answer to Dr Hassin's question, the upward migration of the spinal cord is greatest in utero and in early infancy, therefore fixation of the spinal cord in an adult by a fracture of the spine or a callus does not lead to the formation of an Arnold-Chiari deformity

Structural Changes in the Brain in Experimental Concussion

DR W F WINDLE, DR R A GROAT and DR C A FOX

Concussion is a transient state which sets in immediately on application of an adequate force to the brain Its chief functional manifestations are unconsciousness and paralysis of certain neural components Its histopathologic counterpart is a subtle intraneuronal disorganization In cases of head injuries concussion is often combined with traumatic interstitial hemorrhage, contusion or laceration of the brain We are not concerned with the latter types of injury, for we are dealing with simple, uncomplicated concussion produced experimentally in guinea pigs, cats and monkeys, usually under the influence of light anesthesia induced with chloralosane (preparation of chloral and dextrose) Our present report deals with changes in the central nervous system of these animals during concussion and with the cytopathologic sequelae after concussion

We produced concussion by applying adequate force to the brain, either by means of a pendulum striking the head or through a hydraulic system connecting with the interior of the cranium Our criteria of concussion were cessation of respiration and abolition of the corneal reflex Electrical stimulation within the cat's brain by means of fine electrodes placed with the Horsley-Clarke instrument revealed the following facts The excitability of nerve fibers was relatively unimpaired in concussion, the excitability of cranial motor nerve nuclei was impaired less frequently, to a smaller degree and for shorter intervals than that of supranuclear motor parts, such as the tegmentum of the brain stem, the hypothalamus and the motor cortex Similar differential functional alterations have likewise been observed in rhesus monkeys subjected to concussion Throughout our studies concussional changes in function set in at the moment the blow was delivered Recovery of function occurred gradually

Brains of guinea pigs and rhesus monkeys which were subjected to concussion were prepared for histologic examination Staining was carefully controlled In a few experiments the brain was fixed by perfusion with dilute solution of formaldehyde U S P within a few seconds of the time the concussive blow was struck Significant alterations in arrangement, shape and size of Nissl bodies of neurons were observed in these specimens The Nissl bodies of some cells were fragmented and disarranged by the blow In others they were clumped together as though agglutinated Many neurons seemed to be unaffected

In less than twenty-four hours after concussion chromatolysis of certain neurons began Many cells showed marked changes in two days, reaching maximum intensity by the sixth to the eighth day Progressive chromatolysis culminated in destruction of some neurons, but not all were affected to such an extreme degree Not all neurons were affected equally by concussion Primary afferent and primary efferent neurons of the cranial ganglia and cranial motor nerve nuclei were practically unaffected It was easier to see changes in large than in small interneurons, although the latter were affected too All concussive blows induced changes in the lateral vestibular nuclei and scattered large neurons of the tegmentum of the brain stem With increasing intensity of concussion, the red nuclei, the nuclei of the trigeminal spinal tract and the medial vestibular and cochlear nuclei became involved In the cerebrum, the large pyramidal cells underwent alteration in structure, but they did not show chromatolysis The basal ganglia and the cerebellar cortex appeared to be unaffected The amount of damage was proportional to the strength and the number of blows struck

Concussive blows delivered at intervals of one week in guinea pigs produced as much as 50 per cent loss of neurons at such places as Deiters' nucleus and the red nucleus No loss of cells occurred in primary motor nerve nuclei

In most of our experiments, nerve fibers and myelin sheaths appeared to have received little damage In the specimens which were struck the most severe blows, a variable amount of swelling was observed in the myelin sheaths, especially in the lower part of the medulla oblongata and the upper cervical portion of the spinal cord With the Marchi degeneration technic, changes in myelin sheaths could be demonstrated after severe concussive blows

Simple concussion produced no vascular changes The water content of the brain was insignificantly increased Effects of concussion were not those of asphyxia A significant difference between the effect of concussion and that of cutting the axon was observed

DISCUSSION

DR R A GROAT The only thing I might add is a statement about the relationship between anatomic and functional alterations The distribution of concussional and postconcussional anatomic changes corresponded well with the distribution of concussional functional changes which we found in previous studies in cats Whether or not the relationship between the anatomic and the functional changes which we have demonstrated is causal we cannot say All we can say is that the cell changes indicate the ravages of a concussional force

DR GEORGE B HASSIN Changes of nerve cells following concussion have been observed in the human spinal cord, but not in the brain, where changes have been studied only experimentally The authors' demonstration should be convincing that concussion may bring on almost total destruction of nerve cells in the brains of rabbits In some of them, the changes were pronounced within six days after the lesion, while in the spinal cord of rabbits changes from concussion occurred sometimes within the first twenty-four hours (Ferraro, A Experimental Medullary Concussion of the Spinal Cord in Rabbits, ARCH NEUROL & PSYCHIAT **18** 356 [Sept] 1927) The authors demonstrated only parenchymatous changes and said nothing of the condition of the glia which produces edema in brains with traumatic lesions Nor were the vascular changes, such as hemorrhages, emphasized They were evidently absent In any discussions of cerebral lesions—contusion or concussion—hemorrhage is always mentioned Whether hemorrhages occur in cases of cerebral concussion in human beings is not possible to tell, as such cases have not been studied pathologically It is admitted that concussion always accompanies contusion, but it is hard sometimes to tell which changes are due to the effects of concussion and which to those of contusion In experimental work the task is easier, and one should be satisfied to know that concussion may cause disappearance of nerve cells

DR R P MACKAY Were any histologic studies made on animals with subconcussive blows? Those of us who see patients with minor head injuries are often struck by the relatively serious functional (physiologic) changes which may result, such as severe headache, postural vertigo and "nervous" reactions These symptoms are not psychogenic, even though actual concussion seemed not to have occurred, since the patient did not lose consciousness It would be helpful in courts of law to know of any anatomic or pathologic changes to which such phenomena could be referred

DR A EARL WALKER I have followed this work with interest It is a beautifully controlled study, one that has convinced us that cerebral concussion can be associated with histologic changes in the brain I wonder whether these alterations may not be present in other parts of the brain The cells shown had well formed Nissl bodies In the smaller cells might there not be similar changes that could not be demonstrated by the present technics? There is also this point, that the nuclei involved are in that part of the brain where maximum stresses from a blow occur and where vascular effects are frequently found All are acquainted with Duret's petechial hemorrhages, which occur in the floor of the fourth ventricle I also wish to ask whether there were changes in the hypothalamus, since this region has been said to be involved in concussion

DR VICTOR E GONDA Did tremor occur in these animals, or did they survive long enough for it to be noticed? In boxers exposed to concussion somewhat similar to the type you describe there are many cases in which a typical Parkinson syndrome develops Did these animals live long enough for this to be seen? Were the basal ganglia examined as to changes which might develop at a longer period after injury?

DR W F WINDLE I might say in answer to Dr Hassin's question that the cases we discussed were those in which there were no hemorrhages, although in a few other specimens much stronger blows did produce hemorrhages This picture of concussion is usually produced without any hemorrhage Unlike our studies on the effects of asphyxia, in which marked glial proliferation occurred, we saw no such proliferation after concussion

The question of edema, of course, comes up We have recently run a series of experiments on the water content of the brain It is interesting to note that we did find a little increase in the water content of the brain, but very little In fact, after severe concussion in the guinea pig brain we found that it amounted to 0 5 per cent of the wet brain weight, of about 19 mg, or less than ½ drop

Dr Mackay asked about subconcussive blows We did have animals which were given subconcussive blows A single strong concussive blow led to extensive changes A single light blow did not produce demonstrable changes, but when we superimposed other light blows

we obtained changes similar to those which followed a single concussive blow

Dr Walker asked about cells in other parts of the brain being affected With careful search many small cells can be found showing similar changes We simply demonstrated the larger cells because they are easier to photograph We have not been satisfied that the histologic changes are the result of torsion and shearing of the brain in concussion If such torsion does produce cellular damage, I should expect to see primary motor and sensory nerve cells involved, but this is not the case Alterations after concussion were not periventricular

We found evidence of functional alteration in the hypothalamus, but no structural changes have been demonstrated, perhaps we have not searched closely enough

In reply to Dr Gonda, we saw no tremors The punch-drunk fighter we are not prepared to discuss at this time We have some studies in progress on the cumulative effects of concussion I cannot say anything about the basal ganglia in boxers

Tridione A New Experimental Drug for Treatment of Convulsive and Related Disorders I Pharmacologic Aspects DR. R K RICHARDS

In testing drugs for their possible value in human disease, the pharmacologist is almost always confronted with two principal handicaps first, the innate differences of species in their reaction to drugs, and, second, the fact that in almost every instance the artificial condition created to test the drug differs from the pathologic condition which the drug is supposed to cure Much of the pathology and nature of idiopathic epilepsy and related disorders is unknown, and investigators are still far from creating similar conditions in animals, although epileptoid seizures do occur spontaneously in some species The testing for anticonvulsive properties is based on the production of convulsions by two principal means drugs and electric shock

The fact that a drug will suppress or prevent seizures induced by either of these methods in animals is not sufficient to indicate its usefulness in human therapeutics Most depressant drugs in hypnotic doses are able to antagonize chemically induced convulsions or raise the threshold of the current necessary to produce a seizure However, one must demand a greater specificity than is indicated by mere depression, inasmuch as such drugs frequently produce too great drowsiness in effective doses to be useful in therapeutics

Tridione (3,5,5-trimethyloxazolidine-2,4-dione) was first studied as an analgesic and possesses considerable analgesic properties, these have been substantiated by animal experiments, as well as by clinical observations In a study of a series of antispasmodic drugs which, in toxic doses, produced signs of marked central stimulation and convulsions in animals, it was noted that this compound, Tridione, was remarkably active in reducing convulsions due to the antispasmodics This observation led to more intensive study of the anticonvulsant properties of Tridione In its evaluation, both the drug and the shock method have been used to produce convulsions, although the chemical method seems preferable The anticonvulsant should protect against convulsive, or even fatal, doses of a central stimulant in a dose which would not significantly impair the normal behavior of the test animals Mice and cats have chiefly been used in this study, and metrazol has been found most useful as the convulsive agent

The reaction of mice to metrazol and other convulsant drugs was shown by slides, together with the protective action of various dose levels of Tridione if given before the convulsant If convulsions were produced first, an injection of Tridione almost instantly stopped them and saved the animal's life An effective dose of Tridione would protect mice for about one hour against a certainly convulsive dose of metrazol Phenobarbital, also known to be active against metrazol, was found to be somewhat more depressant than Tridione Diphenylhydantoin has been reported to protect against metrazol convulsions only if administered for several days before the injection of the convulsant The observations on cats substantiated those on mice

In some studies convulsions were produced in rats by placing the electrodes on the head and using various voltages of the secondary coil of a Harvard inductorium to induce convulsions The tests were rather crude, the thresholds referring to the prevention of full blown convulsions only Tridione is effective in raising the threshold necessary to produce convulsions, this is also true of phenobarbital and diphenylhydantoin In these studies, also, phenobarbital produced a greater depression than Tridione

Even in view of the demonstrated activity of Tridione in experimentally induced convulsions, the proof of its therapeutic value must rest in the hands of the clinician

II Clinical Investigations DR M A PERLSTEIN

This study represents a total of 47 patients who have been observed over a period of eight months, in the Children's Neurologic Clinic of Cook County Hospital, the Cerebral Palsy Center of St John's Hospital, Springfield, Ill, and in private practice

The distribution of cases according to diagnosis and the results obtained are indicated in the accompanying table

Effects of Administration of Tridione to 47 Patients with Various Neurologic Diseases

	Number of Patients	Benefit	
		Considerable	Slight or None
Epilepsy			
With organic cerebral disease			
Grand mal	5	1	4
Petit mal	1	0	1
Both grand and petit mal	5	0	5
Total	11	1	10
Idiopathic epilepsy			
Grand mal	5	4	1
Petit mal	6	5	1
Both grand and petit mal	1	0	1
Total	12	9	3
Cerebral palsy			
Spastic	3	1	2
Athetoid	7	7	0
Dystonia musculorum	2	0	2
Total	12	8	4
Behavior disturbance	6	5	1
Tetanus	4	2	2
Chorea	2	0	2

Epilepsy—Electroencephalographic studies on many of these patients before and after administration of Tridione showed improvement in the tracings after the administration of Tridione, in general paralleling the clinical response From the table it is seen that when there is definite organic disease of the brain Tridione is of little, or no, benefit When the symptoms are on an idiopathic basis, Tridione seems to be of considerable

value, or at least the equal of diphenylhydantoin and phenobarbital Its greatest value was noted in the petit mal types, in which diphenylhydantoin and phenobarbital often aggravate the condition

Cerebral Palsy—In this series, 12 children with cerebral palsy were given Tridione for relaxation prior to institution of physical therapy The greatest benefit was noted in patients with the athetoid form All 7 children showed a considerable degree of relaxation The spastic patients did not respond to the drug Of the 2 patients with dystonia, 1 had a congenital condition and responded slightly to treatment, and in the other, with the acquired form, the drug aggravated the symptoms

Thus the drug seems to be of benefit in producing relaxation of the tension of the athetoid type but fails to have any effect on the spastic form

Functional Disturbances—In this series, 4 patients presented serious behavior disturbances, such as stealing, running away from home and committing arson All showed pronounced improvement with Tridione One patient, who was included in the epilepsy group, had grand mal seizures which were controlled with diphenylhydantoin, and the behavior disturbance was effectively treated with a single daily dose of 10 grains (0 65 Gm) of Tridione

Chorea—Two patients with chorea were treated with Tridione, with equivocal results It was felt that the drug was of no greater value than phenobarbital

Tetanus—Four patients with tetanus were treated, 2 children and 2 adults The drug was administered intravenously in 1 Gm doses, with the object of stopping convulsions and spasms The 2 adults had severe alcoholism, and although Tridione was effective in stopping the spasms, its action was only transitory In the 2 children the drug was effective in controlling the convulsions However, 1 child was in a terminal state on admission and died within twenty-four hours The other child recovered

Conclusions—A new drug, Tridione, is reported, the action of which seems to be greatest in controlling those symptoms, convulsive or otherwise, in which the pyramidal tracts are not involved

In treatment of convulsions due to organic disease of the brain or of cerebral palsy due to involvement of the pyramidal tract or its cells of origin, Tridione seems to be of some value, although not as much so as phenobarbital or diphenylhydantoin

In treatment of convulsions of idiopathic origin, disturbances of behavior or cerebral palsy in cases in which the lesion is presumably extrapyramidal, the drug is of definite value In management of petit mal the drug is of greater benefit than other drugs hitherto used

In treatment of chorea the drug is of no value

In treatment of tetanus it shows definite promise, and further investigation should be made

Tridione has a low toxicity and is well tolerated in massive doses by both children and adults over a relatively long period No side effects were noted in this series The doses used varied from 5 to 10 grains (0 325 to 0 65 Gm) three to four times daily

DISCUSSION

DR F A GIBBS The authors of this exceedingly interesting paper have shown that Tridione has practical therapeutic value When it was found that certain persons did not respond to large doses of phenobarbital or diphenylhydantoin, alone or in combination, I am sure many of us concerned with the investigation of epilepsy felt that we were at the end of our rope This new drug offers new possibilities The fact that it is not particularly valuable in cases of organic damage to the brain is not a serious limitation to its usefulness, for the great bulk of epileptic patients are without evidence of organic cerebral damage, nor is the statement that it is better for petit mal than for grand mal a serious disparagement Petit mal can be extremely incapacitating, particularly with patients who drop to the ground with each attack or in whom the attacks come so close together that the condition can be referred to as petit mal status The best anticonvulsant available, diphenylhydantoin, is not only relatively ineffective against petit mal but in many cases exacerbates it I have had patients ask to be taken off treatment with diphenylhydantoin because they would rather be unconscious for a few minutes once a month with grand mal than unconscious all the time, i e, be in petit mal status If Tridione can be used to control petit mal, either alone or in combination with other drugs, it will be an exceedingly valuable remedy

Dr Perlstein has indicated that this is a preliminary report, and the electroencephalographic phase of the study was not supposed to be of major importance, the question at issue being whether Tridione does or does not have a therapeutic effect on clinical epilepsy However, the authors are wise to have classified their cases, both clinically and electroencephalographically, in an effort to determine whether the drug has more value for one type of disease than another, and I agree that there is also advantage to be derived from knowing whether the drug entirely corrects the underlying cerebral dysrhythmia or merely prevents the most severe paroxysms of dysrhythmia, which externalize themselves in clinically obvious seizures

DR CLARENCE NEYMANN I should like to ask about the measurement of the electrical currents No doubt the authors know that the amount of current depends on the voltage times the amperage divided by the resistance It is known that Ohm's law does not apply to organic substances and that in living organic substances the resistance decreases as the current continues to pass through the tissues The currents employed were much more intense than those ordinarily used therapeutically I should like to ask whether this was the intent of the experiment and whether the ohms of resistance were observed after the shock, also I should like to inquire of Dr Perlstein whether the drug has been tried in cases of paralysis agitans following lethargic encephalitis

DR R K RICHARDS As I tried to point out, these experiments were rather crude The inductorium voltages were calibrated by a competent physicist The current source was always the same, a 2 volt dry cell The period of stimulation was probably too long Further electroshock studies are being made with more refined technics, but I do not have the complete reports at this time No particular significance is attached to the absolute voltage values The important point is the sharp increase in threshold obtained after administering the drug

DR M A PERLSTEIN This material is unquestionably overweighted with cases of convulsions due to organic disease of the brain because of the children seen in Cook County Hospital Children's Neurology Clinic there are many with lead poisoning, postinfectious encephalitis, head trauma and other organic conditions of the brain which result in recurrent convulsions As pointed out by Dr Gibbs, in most clinics devoted to epilepsy the number of cases of the idiopathic form would undoubtedly be higher

I have not had any cases of paralysis agitans in this series, but many of the behavior conditions in children were postencephalitic, and this might indicate the possibilities of the drug in treatment of paralysis agitans

ALEX J ARIEFF, M D, *Vice President, in the Chair*

Regular Meeting, Feb 13, 1945

Serous Meningitis DR H C VORIS

There is a heterogeneous group of patients who show evidence of increased intracranial pressure but who prove not to have a space-occupying lesion Some of these patients have a history of infection contiguous to the intracranial cavity, in the ear, mastoid or sinuses They are suspected of having a cerebral abscess A few have had an injury to the head and are thought to have a subdural hematoma Others have no history of infection or injury and are considered to have a brain tumor

Six cases were presented in some detail to illustrate some of the problems encountered in cases of a condition which can be briefly described as characterized by subjective symptoms suggesting increased intracranial pressure and papilledema Neurologic signs, exclusive of those associated with increased intracranial pressure, are minimal, and definite localization is seldom suggested Other types of cases were briefly discussed, and a classification was indicated

The author reported 43 personal cases in which intracranial exploration revealed no neoplasm or abscess and the diagnosis of serous meningitis or its equivalent had been made The lack of adequate pathologic study in this series, as well as in most of the series reported, was mentioned This absence of pathologic data is partly explained by the difficulty of getting adequate biopsy material at operation The need for further microscopic studies in cases of serous arachnoiditis was emphasized

DISCUSSION

DR PAUL C BUCY This interesting group of cases is uniform only in the confusion they cause members of the medical profession Certainly, there is a variety of causes which produce this general picture One or two might be added to the list Dr Voris presents In many cases of aural infection thrombosis of the lateral sinus or of the veins of the cerebral cortex produces pressure similar to this Often, when there is evidence of localized cerebral involvement, differentiation from cerebral abscess may be most difficult

I have previously pointed out to members of this society that lead poisoning may also give rise to this picture of increased intracranial pressure In 1 of the cases presented by Dr Voris I believe the lateral roentgenogram of the skull gives a clue to the pathologic process It will be noted that the attachment of the tentorium is pushed up higher than normal This appearance is indicative of congenital atresia of the foramens of Magendie and Luschka At operation one finds pronounced dilatation of the fourth ventricle, as Dr Voris did in this case The tentorium is curved upward in the center, and thus the occipital horns of the lateral ventricles, which lie laterally, are visible below the level of the central portion of the tentorium Such displacement of the tentorium occurs only when the atresia of the foramens of the fourth ventricle is congenital

DR FREDERICK HILLER Why do the symptoms sometimes appear so late if the atresia is congenital?

DR PAUL C BUCY I wish I knew why this is so I have seen atresia of the aqueduct give rise to increased intracranial pressure in the teen age group This patient was 14 years old I presume it is because the occlusion is not complete

DR HAROLD C VORIS Dr Bucy's suggestion regarding the case I have reported as an instance of arachnoiditis of the posterior cistern is very interesting Unfortunately, I did not take a biopsy specimen of the arachnoid at the first operation, so that the clinical diagnosis of arachnoiditis remains unverified

Anatomic Contribution to the Problems of Perception, Awareness and Attention DR ADOLF WALLENBERG (by invitation)

The Electroencephalographic Pattern of Encephalitis DR F A GIBBS and MRS E L GIBBS (by invitation)

Six channel electroencephalograms have been obtained in 133 cases of encephalitis of undetermined and specific types In some cases single studies were made, and in others repeated examinations were carried out at varying intervals In the acute phase a high degree of electroencephalographic abnormality is almost invariably present, even though the clinical symptoms are only moderately severe In the subacute phase less extreme forms of abnormality occur, and, as might be expected, seizure discharges are commoner in persons who have seizures than in those who have not, the latter group shows a relatively high incidence of normal electroencephalograms In the postencephalitic phase the electroencephalogram shows seizure discharges and exceedingly slow activity in persons in whom seizures have developed Other patients, even those with severe paralysis agitans or oculogyric crises, usually have normal electroencephalograms Epilepsy is a much commoner sequel of encephalitis in children than in adults Postencephalitic epilepsy is much commoner in children than in adults That such a condition is not misdiagnosed as idiopathic epilepsy is indicated by the fact that electroencephalograms of persons with this type of epilepsy usually show focal abnormalities, whereas the electroencephalograms of persons with idiopathic epilepsy do not

DISCUSSION

DR CHESTER DARROW I should like to express appreciation of Dr Gibbs's clear presentation and to ask whether he has observed any differential characteristic of so-called postencephalitic behavior My associates and I have been particularly interested in this problem

DR A EARL WALKER How accurately can one prophesy from the electroencephalogram whether or not a patient with the acute stage of encephalitis will later have epileptic attacks?

DR PAUL C BUCY I should like to ask whether it is possible to differentiate the slow waves seen in the case of encephalitis from those seen in the case of cerebral neoplasms, without regard, of course, to the progressive changes seen in successive electroencephalograms

DR F A GIBBS Dr Darrow asks about the incidence of electroencephalographic abnormality in children with behavior problems When there is evidence of epilepsy, encephalitis or organic damage to the brain, the incidence of electroencephalographic abnormality is high When this is absent and the behavior disorder itself is not of an epileptic, postencephalitic or organic type, the incidence of electroencephalographic abnormality is no higher than that in the control group

Dr Walker's question should be answered in the negative, in the acute phase it is impossible to say who is and who is not going to have epilepsy

Dr Bucy has asked about the specificity of the electroencephalogram for a particular type of lesion It has

almost no specificity, but in certain cases tumor can be ruled out because the abnormality steadily increases, or decreases in one spot and increases in another

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D GAMMON, M D *Presiding*
Regular Meeting, Jan 26 1945

Surgical Treatment of Spontaneous Nontraumatic Hematoma of the Left Temporal Lobe Report of Three Cases DR MICHAEL SCOTT

Three cases of spontaneous hematoma of the left temporal lobe were reported in which the following syndrome was present sudden onset with severe headache or aphasia, progressive drowsiness, and focal signs of involvement of the left temporal lobe, namely, (*a*) mixed aphasia with anomia and jargon speech, (*b*) right homonymous hemianopsia, (*c*) increased tendon reflexes on the right, (*d*) Hoffmann and Babinski signs on the right, (*e*) progressive weakness of the right side of the body, (*f*) absence of sensory disturbance and (*g*) shift of the pineal gland to the right The spinal fluid pressure was usually increased and the fluid was blood tinged, clear or xanthochromic The total protein was always higher than normal

An exploratory craniotomy on the left side revealed a subcortical hematoma in the posterior superior portion of the temporal lobe on the same side in all 3 cases The clot was removed by suction, the dura closed and the bone flap replaced Recovery with improvement took place in all 3 cases

A series of 12 similar cases reported by various authors was reviewed The symptoms in these cases fell into the same pattern as that just described No definite etiologic factor could be found Excitement and overexertion appeared to be the precipitating factors In most cases studies concerned with exogenous toxins, blood dyscrasias and virus and other forms of infections were inadequate

Conclusions—Intracerebral hematoma of the left temporal lobe gives rise to a syndrome characteristic of an acute focal expanding intracranial lesion

This condition is often erroneously diagnosed as a "stroke" resulting from cerebral arteriosclerosis or hypertension

Exploratory craniotomy with evacuation of the blood clot offers the best method of treatment in cases showing progression of focal signs and increased intracranial pressure

DISCUSSION

DR ANTHONY S TORNAY I had the opportunity of seeing the second patient presented by Dr Scott I first saw her several days after her admission to the hospital, and I made the clinical diagnosis of spontaneous subarachnoid hemorrhage Later the first evidence of elevation of the optic disk was noted, and I suggested the possibility of a neoplasm into which a hemorrhage had taken place Dr Scott was asked to see the patient I was much surprised and pleased with the results of his examination After the patient came back from the surgical department, she complained of considerable headache As days passed, she did not seem to be doing well She was placed on a dry diet, and several spinal taps were made I thought a second operation might have to be done However, her husband solved the problem by removing her from the hospital, so I don't know what eventually happened I did not diagnose the condition accurately This presentation brings to the attention of the society the fact that such a condition may exist and that one should be mindful of it

DR SHERMAN F GUPIN It seems to me that the important thing is the making of the correct diagnosis In case 1 I thought only of a vascular accident, when the roentgenogram showed a shift of the pineal gland, I did not think of an intracerebral clot In another case there was choking of the disk I do not remember the special feature of the third case, but something took all these cases out of the ordinary run of cases of vascular accidents I am wondering whether there are not other cases which are unrecognized because there does not happen to be a choked disk or a shift of the pineal gland

I cannot resist commenting on another point, although it is not particularly apropos, and that is the total protein values of the spinal fluid These values have been interesting and and troubling me for some time They were discussed at the meeting of the American Neurological Association this summer I think it was a medical man who reported on observations on the spinal fluid in 100 normal subjects A large percentage of these persons showed an increase of total proteins, and they had no indication of the presence of any neurologic disease This certainly makes one wonder what significance one may attach to these elevated protein values

DR NATHAN S SCHLEZINGER In view of the apparent rarity of the condition, of which Dr Scott found only 14 cases reported in the literature, I think another case ought to be recorded A woman aged 22 was admitted to the Jefferson Hospital in May 1943 This patient presented the same condition as that described here except that her lesion was on the right side of the brain The onset was acute, and typical of subarachnoid hemorrhage, in addition, there was complete left hemiplegia The eyegrounds were normal The spinal fluid pressure was increased to about 300 mm in the early stage About ten days after the onset the patient began to have headaches In the meantime she had mental confusion, but this cleared up She complained of severe headaches The eyegrounds began to show papilledema, which increased to a level of about 4 D within three weeks after the onset The spinal fluid pressure reached 660 mm , a liquid hematoma was removed at operation Subsequently, there was a gradual and rather notable improvement, so that now, approximately two years after the onset, the patient is able to carry on a fairly normal life, including dancing This patient was 22 years old, I do not know the average age in the cases reported This case differs from the 3 cases reported by Dr Scott in that the right side of the brain was affected

DR GEORGE D GAMMON Is the location of these hemorrhages particularly characteristic, and do they differ in any way from other cerebral hemorrhages? If not, what are the indications for operative treatment of intracerebral hemorrhage?

DR MICHAEL SCOTT I shall answer Dr Gammon's question first In all these cases a similar part of the temporal lobe was involved, as shown by the position of the silver clips in the postoperative roentgenograms Naffziger, in a discussion on a paper by Craig and Adson, pointed out that in his experience both the traumatic and the spontaneous hematomas had a predilection for this portion of the temporal lobe

The indication for operation is a progressive increase in intracranial pressure and focal signs The patient has his initial symptoms, gets better for a while and then suddenly begins to grow worse, with severe headaches and signs of persistent increase in intracranial pressure and paralysis

I was glad to hear the discussion concerning what would happen if these patients were not operated on There are cases of intracerebral hemorrhage in which bleeding stops, the symptoms gradually abate, the clot becomes cystic and an intracerebral scar results On the other hand, when there is definite evidence of progressive increase in focal signs, intracranial pressure and choked disk, I feel that one is justified in making an exploration I see no reason that calcium should not be deposited in these areas of hemorrhage months or years after its occurrence It was not seen or reported in the 15 cases reviewed tonight

Dr Gilpin's point about the relative importance of the pineal gland as a diagnostic aid is a pertinent one, because in many persons the pineal gland is not calcified It was not calcified in the second case of this series Of the 12 cases of hematoma in the left temporal lobe which were reported in the literature, a roentgenogram of the skull was mentioned in only 1, and that was reported as normal In 2 cases air studies were made One cannot deny the diagnostic value of a shift of the pineal gland when it is over 3 mm The paper read tonight was restricted to hematomas of the left temporal lobe I must emphasize that these hemorrhages may occur in any other lobe and may give rise to focal symptoms characteristic of that area

Book Reviews

Textbook of Neuropathology. Second edition By Arthur Weil, M D Price, $5 Pp 356 New York Grune & Stratton, Inc, 1945

In his preface to the second edition of this textbook, the author admits that while great strides have been made in neuropsychiatry, especially therapeutically, since he published his first edition, neuropathology as such has not been affected by these discoveries He feels that "most of the contributions to neuropathology have been made in the experimental field, the investigation of the vitamin deficiencies, the experimental production of tumors of nervous tissues, and the experimental study of the pathology of the different shock treatments" It is therefore to these newer additions that the reader turns his attention, only to discover that in the whole book of 356 pages, 5 to 10 pages at most are devoted to the newer works referred to by the author The material dealing with vitamin deficiencies and shock treatments is rather abbreviated The data dealing with the experimental production of tumors are presented in somewhat more detail, perhaps because the author has been very active in this field of study For that matter, his well known interest in the chemistry of the nervous system makes itself evident throughout the book, and from that angle the work presents a departure in orientation from the usual textbooks of neuropathology

The book as a whole is readable, although in some spots it falls prey to the nemesis of most textbooks—that is the listing off in the text proper of works by other authors, without elaboration There is, however, a minimum of this, and at the end of the book is a fairly good bibliography, arranged according to subject matter, for those who are interested in further reading The author reveals here and there a freedom of thinking which tries to break through the fetters of classic and conventional neuropathology, but he ruefully admits that he is limited by the confines of his subject, especially as far as classification is concerned

One criticism which could be leveled at this book, as well as at pathologic texts in general, is that whereas many of the pictures may mean something to the pathologist, unless there is a complete legend, with specific designation of the exact areas referred to, they usually represent a meaningless splotch to the young clinician

In the main, this book is satisfactory and should meet the needs of the practicing neurologist

The Falling Sickness A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology By Owsei Temkin Price $4 Pp 324, with index and illustrations Baltimore Johns Hopkins Press, 1945

In grasping and dealing with difficult concepts, a consideration of their history is a great, sometimes an essential, aid For the first time, a scholarly, definitive history of the development of knowledge of epilepsy is made available, and every student of the subject should read it with care In a work bristling with references and verbatim quotations, Dr Temkin leads his readers from fragmentary references to convulsions in the literature of antiquity to a careful study of the philosophic and physiologic theories of Jackson and Charcot

Many interesting bits of information are to be gathered on the way The reference to epilepsy in the Code of Hammurabi is vague and of questionable authenticity Unilateral seizures were mentioned by Hippocrates and were well described by Aretaeus, who stated that they could sometimes be controlled by sensory stimulation of the affected part Hippocrates referred to epilepsy at one point as "the great disease," and this is apparently the origin of the term "grand mal" Aristotle first called attention to the incidence of epilepsy among distinguished characters of history Galen coined the term "aura," because one of his patients complained of a feeling like a breeze blowing on one extremity before loss of consciousness occurred Galen further made a distinction between epilepsy due to an idiopathic disease of the brain and that due to "sympathetic" involvement, secondary to disease elsewhere in the body

The confusion between the disease epilepsy and, first, witchcraft and, later, hysteria and a fantastic empiric polypharmacy beclouded the entire subject from the time of the giants of antiquity to the nineteenth century Dr Temkin's account of the development of modern conceptions is far too complicated and detailed to permit abstraction

Dr Temkin accepts the diagnosis of epilepsy for Julius Caesar, Caligula, Petrarca, Charles V, Torquato and Mohammed It is a matter of some regret that one does not have his opinion on the authenticity of the diagnosis for other distinguished men, for example, Napoleon and Peter the Great

This volume was financed by the Epilepsy Medical Research Fund of Johns Hopkins University, and it constitutes a most important contribution to the subject

Diseases of the Nervous System in Infancy, Childhood and Adolescence Second edition By Frank R Ford, M D, Associate Professor of Neurology, Johns Hopkins University Price, $12 50 Pp 1143 Springfield, Ill Charles C Thomas, Publisher, 1945

This book is that comparative rarity, a definitive work in its field The first edition gained wide recognition for its authority, and the new volume contains additional material on such topics, among many, as hemorrhagic disease of the newborn and disorders of lipid metabolism

The first chapter is concerned with the examination of the nervous system, especially its modification in testing children The various aids to neurologic diagnosis, such as roentgenography and electroencephalography, are also thoroughly described

The vast bulk of the book is devoted to descriptions of the various neurologic syndromes and disease entities Throughout, the style is lucid, the references are numerous and easily accessible and the illustrations frequent and enlightening

One might wish for more material on certain psychiatric aspects of neurologic conditions, for example, the behavior disorders of children following head injury But since such material is at the present time largely speculative and conjectural, one respects Dr Ford's right to omit such discussions from his work

The book is unqualifiedly and enthusiastieally recommended to any one interested in the neurologie disorders of the young

Distonia de torção By A Austregesilo Jr Pp 316, with 133 illustrations and bibliography Rio de Janeiro Irmãos di Giorgio & Cia, 1945

This thesis, in the classie style, details personal observations in 5 eases and eovers the literature in sketchy style Most of the illustrations dealing with the pathologie anatomy, 47 from a single case, are uneonvineing, while 20 additional photographs of a patient in various attitudes are too small to permit aeeurate analysis of the patterns of muscular activity The ease reports are padded with unessential information It is doubtful whether the sixteen pages of referenees have been cheeked with the original artieles Aside from revealing the fact that dystonia occurs in Brazil, this monograph eannot be said to add much to knowledge of the subject It is to be hoped that the author will break with tradition in his next volume and dig below the surfaee, the present work refleets no great credit on Brazilian neurology

Egas Moniz Ultima lição, bibliográfia Pp 86 Lisbon, Portugali i, 1944

This is the swan-song of Egas Moniz, who retired from the field of teaching in November 1944 It is a review of his work, an apology and an acknowledgment to those who have been associated with him It is written in the elegant prose which the author has applied to other fields besides medicine The bibliography includes 324 titles, including books on medieal history, art, polities and geography, for Egas Moniz was an essayist and critic as well as a physician The two major contributions of Egas Moniz are described, fortunately, in the first person As he says, it is of special interest to readers to know what led up to the experiments and how the preliminary steps were made Egas Moniz gives mueh more space to his work with eerebral angiography than he does to prefrontal leukotomy In making his farewell, he looks forward to the changes that will eome about in the field of medicine and leaves that field to younger men

Character-Analysis Principles and Technique for Psychoanalysts in Practice and in Training By Wilhelm Reich, M D Translated by Theodore P Wolfe Seeond edition Price, $4 50 Pp 324 New York Orgone Institute Press, Inc, 1945

As the subtitle indieates, the book is of primary interest to psychoanalysts It is an exeellent study of the problems of teehnie Reich's exposition of his thesis is clear and penetrating Mueh of the material on eharacter analysis is part and pareel of present day analytie proeedure The diseussions of the many problems that arise in psychoanalytic praetice are clear and instruetive His aeeount of the differenees between neurotie symptoms and character problems is clear and eogent The author stresses the need of knowledge about the orgasm and its psyehic function His disagreement with Freud's eoneept of the death instinct as an explanation of masoehism is presented His own theoretie coneeption of the origin of masoehism is well stated

The footnotes relate to Reieh's more reeent work with the Orgone, but they ean be easily disregarded by the reader They merely intensify one's regret that so able a worker wanders so far from scientifie studies of human behavior

Mental Disorders in Later Life Edited by Oscar J Kaplan, Ph D Price, $5 Pp 436 Stanford University, Calif Stanford University Press, 1945

The fact that more people are continuing to live into old age is of great importanee to psyehiatry, as well as to general medieine It is neeessary to reevaluate the knowledge that exists eoncerning the faetors bearing on the mental health and mental disease of this older age group In general medicine, as well as in psychiatry, there have been too long a fatalistie attitude toward the ills of the aged and a laek of therapeutic initiative

This volume eontains a compilation to date of the knowledge eoncerning the mental disturbanees of the elderly and some of the physieal and emotional factors involved in producing them The chapter on the physiologic aspects of mental disorders in later life, by Nathan W Shock, is partieularly good He eoncludes that there is in the aged a progressive loss in the homeostatic capaeities of the organism It is true that in old people hemostasis is often maintained, but only by utilizing reserve meehanisms It is pointed out that researeh is needed in determining the amount of "physiologic stress" required to bring out these secondary meehanisms

There is a good evaluation of the psychologie characteristics of aging and of the aged and the role these factors play in mental disorder The sociologic aspects of the aged are reviewed, and the immensity of the problem is pointed out There are totally inadequate cultural institutions for taking into consideration the needs, both physieal and emotional, of old people For proper mental hygiene and preventive psyehiatry these aspeets must be thoroughly explored

The faet that neuroses in old people have a greater incidenee than the psyehoses is not generally appreciated Certainly, mueh is written about the psyehoses and too little about the neuroses of later life Norman Cameron discusses these neuroses rather eomprehensively and indieates patterns of therapy

There are, of eourse, several ehapters eoneerned with the involutional psychoses, the presenile dementias, the senile psychoses and the psychoses associated with eerebral arterioselerosis Psyehosomatic medieine, psyehotherapy and mental hygiene with reference to the older patient are given spaee in this eompendium The material is presented elearly, simply and interestingly Some chapters have an extensive bibliography, and in some there is an attempt to indicate where more researeh is needed

This volume is recommended for use of all psyehiatrists

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IMPORTANCE OF NEURAL FIBROBLASTS IN THE REGENERATION OF NERVE

D DENNY-BROWN, M B
BOSTON

IT IS generally agreed that the regeneration of peripheral nerve is accomplished by the regrowth of axis-cylinders in close relation to the remnants of the Schwann cells of the degenerated nerve Whether the Schwann bands form a medium favoring active growth or provide simply a passive linear path without obstruction is still debated [1] Few [2] deny the Schwann cell any part in the process of conduction of the regenerating fiber There is no doubt, however, that the Schwann nucleus determines the maturation of the myelin sheath at a later stage of restoration When there has been a breach in continuity in the nerve, the outgrowing axis-cylinder bridges the gap, but the factors which aid or hinder this process are imperfectly understood These problems have been reviewed at length by Ramón y Cajal [3] and, more recently, by Young [1] and by Weiss [4] They are of primary importance in all questions relating to nerve grafts, recently reviewed by Sanders,[5] Sanders and Young,[6] Davis and associates,[7] Tarlow and Epstein [8] and Seddon and Holmes [9]

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School

1 Young, J Z The Functional Repair of Nervous Tissue, Physiol Rev. **22** 318-374, 1942

2 Hassin, G B Peripheral Nerves Anatomic and Physiologic Considerations, Arch Neurol & Psychiat **27** 58-78 (Jan) 1932

3 Ramón y Cajal, S Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928

4 Weiss, P The Technology of Nerve Renegeration A Review, Sutureless Tubulation and Related Methods of Nerve Repair, J Neurosurg **1** 400-450, 1944

5 Sanders, F K The Repair of Large Gaps in the Peripheral Nerves, Brain **65** 281-337, 1942

6 Sanders, F K, and Young, J Z The Degeneration and Re-Innervation of Grafted Nerves, J Anat **76**·143-166, 1942

7 Davis, L , Perret, G , Hiller, F , and Carroll, W Experimental Studies of Peripheral Nerve Injuries III A Study of Recovery of Function Following Repair by End-to-End Sutures and Nerve Grafts, Surg , Gynec & Obst **80**: 35-59, 1945

8 Tarlow, I M , and Epstein, J A Nerve Grafts The Importance of an Adequate Blood Supply, J Neurosurg **2** 49-71, 1945

(Footnotes continued on next page)

If the nerve of an animal is severed, the ends retract to some extent Nevertheless, in the absence of obstruction, a fibrous bridge forms between the two ends Across this connecting scar sprouts of axis-cylinders make their way to the cut end of the distal nerve Nageotte [10] discovered that this bridging tissue grew as much from the distal cut end as from the proximal, and in view of its very cellular nature and the tendency of the cells to be associated with fibrils which stained electively with Benda's stain for neuroglia fibrils he claimed its derivation from the Schwann cells of the peripheral segment He called the outgrowth a "peripheral glioma" and, later,[11] a "Schwannoma" He established the identical nature of the outgrowth from the central cut end, here complicated by the addition of regenerating axis-cylinders This view has been supported by many investigators, most recently by Masson [12], Young, Holmes and Sanders [13], Young,[1] and Weiss [1] From the beginning Nageotte recognized that fibroblasts became included in the neural scar and the aim of most methods of grafting or splicing the cut ends of nerves has been to exclude these cells from the union, for the reason that contracting fibrous tissue would eventually strangulate the regenerating nerve fibers

It is therefore surprising that in 1928 Ramon y Cajal,[3] in his excellent and balanced account of this subject, should state (page 183) that from the second day onward the scar is formed of fibroblasts, which after the third day become arranged in bundles of various sizes, often perpendicular to the wound He identified the possession of an endocellular Golgi apparatus by these cells, like that described in ordinary fibroblasts, and indicated his belief in their origin from the plasma cells of Unna, which lie around the preexistent blood vessels

> Concerning the origin of the cells that surround the sprouts of the scar from the sixth day after the operation, we must confess that the investigators of the last few years have not dispelled our doubts and that, for us, the ectodermic deviation of these elements is not a demonstrated and irrefutable truth [page 196] [3]

Cajal and others observed that the nerve sprouts travel in the meshes between the cells of the scar and only at a later date are accompanied

9 Seddon, H J, and Holmes, W The Late Condition of Nerve Homografts in Man, Surg, Gynec & Obst **79** 342-351, 1944

10 Nageotte, J Note sur la presence de fibres nevrogliques dans les nerfs peripheriques degeneres, Compt rend Soc de biol **75** 122-124, 1913

11 Nageotte, J Sheaths of the Peripheral Nerves Nerve Denegeration and Regeneration, in Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, vol 1, sect 5

12 Masson, P Experimental and Spontaneous Schwannomas (Peripheral Gliomas), Am J Path **8** 367-388, 1932

13 Young, J Z, Holmes, W, and Sanders, F K Nerve Regeneration Importance of the Peripheral Stump and the Value of Nerve Grafts, Lancet **2** 128-130, 1940

with Schwann cells, which are oriented along their length and enclose them in cytoplasm Nageotte [11] described the enclosure of the growing sprout in the scar by the Schwann cell at the seventh day, a phenomenon that appears to be possible only in very short scars He further described the formation of membranous septums derived from the envelope of the Schwann cell as a primitive endoneurium "which thenceforth grows and becomes vascularized like any connective tissue Other fibroblasts arrange themselves around the young nerve bunble and among them the lamellated sheath is constructed [page 228] " [11] The fibroblasts were held to penetrate the primitive endoneurium at a late stage Masson [12] described columns of Schwann cells extending from the interior of an explanted piece of nerve into the new tissue at either end and their subdivision by collagen, which he stated is precipitated around the Schwann cell Cajal [3] did not offer any description of the development of a perineurium over the regenerated bundle

In general, the difficulty of establishing good functional union across a gap in nerve increases proportionately to the diameter of the nerve, as well as to the length of the hiatus Small nerves and the nerves of small animals have an astonishing capacity for attaining good functional union across large gaps without any assistance Though such a natural bridge also tends to form in larger nerves, the newly regenerated piece of nerve also remains of small size and, consequently, of limited functional value In human nerve such natural bridges across a gap exceeding about 2 cm are usually valueless It is essential, therefore, that the union tissue should allow redevelopment of a nerve of full size On the basis of experience that the degenerate Schwann tissue of the distal segment of peripheral nerve is the best known conductor of regenerating fibers, the aim of grafting has been to fill the hiatus with such tissue Though the natural nerve scar tissue is supposed by many to be composed of Schwann cells, it tends to grow laterally and form a mass instead of providing tubular conductors Even as cement substance between nerve ends its formation is deprecated on account of its high content of collagen Nerve fibers can certainly grow in neuromas, however, and if more can be learned of factors which lead to their local diffusion and prevent longitudinal development, the healing of neural scars and the bridging of gaps could be improved The factor usually blamed for failure both of end to end sutures and of nerve grafts is fibrosis

The origin of intraneural fibrosis is in some doubt In thick grafts and transplants central necrosis was observed by Maccabruni,[14] Biel-

14 Maccabruni, F Der Denegerationsprozess der Nerven bei homoplastischen und heteroplastischen Propfungen, Folia neurobiol **5** 598-601, 1911

schowsky and Unger [15] and Bunnell and Boyes,[16] and it was found by Sanders and Young [6] and Davis and associates [7] in some homografts but not in autografts On the general pathologic principle that necrosis will progress to fibrosis, some surgeons aim primarily to give the graft a good collateral blood supply either by making a cable of small nerves, with a wider total external surface than that of one large piece, or, recently, by fashioning a fat–areolar tissue flap for the graft [8] Others seek to exclude "connective tissue penetration" [1] by sheathing suture lines, or even the whole graft In view of the abundant outgrowth of tissue from the cut end of nerve, mentioned earlier, the evidence that connective tissue can grow in at this point appears to be weak Further, though vessels grow directly across the nerve ends in simple sutures and into grafts,[17] the supply by this mean is variable, for it was observed to be less in homografts than in autografts Tarlow and Epstein [8] demonstrated the defective vascularization of grafts in tantalum sleeves They found tension also to be a detrimental factor.

My observations and those of my associates on the effect of percussion on peripheral nerve [18] and on the results of sudden stretching [19] have indicated that rupture of the perineurial sheath of a peripheral nerve bundle leads to consequences more grave than those attending drastic intraperineurial damage In perusal of illustrations of Platt,[20] Spielmeyer [21] and others on the pathologic features of neural scars associated with failure of recovery, we have been impressed with the frequent continuity of endoneurial and epineurial fibrosis The missing or fragmentary structure is the intermediate sheath, or perineurium. The present investigation began with an attempt to determine the contribution of perineurium to neural scar tissue and led to inquiry as to the degree to which an intact perineurium conserves the process of regeneration

15 Bielschowsky, M, and Unger, E Die Ueberbruckung grosser Nervenlucken Beitrage zur Kenntnis der Degeneration und Regeneration peripherischer Nerven, J f Psychol u Neurol **22** 267-318, 1918

16 Bunnell, S, and Boyes, J H Nerve Grafts, Am J Surg **44** 64-75, 1939

17 Weiss, P Nerve Regeneration in the Rat Following Tubular Splicing of Severed Nerves, Arch Surg **46** 525-547 (April) 1943 Sanders [5]

18 Denny-Brown, D, and Brenner, C The Effect of Percussion of Nerve, J Neurol, Neurosurg & Psychiat **7** 76-95, 1944

19 Denny-Brown, D, and Doherty, M The Effects of Transient Stretching of Peripheral Nerve, Arch Neurol & Psychiat **54** 116-129 (Aug) 1945

20 Platt, H The Surgery of the Peripheral Nerve Injuries of Warfare, Bristol, John Wright & Sons, 1921

21 Spielmeyer, W Zur Klink und Anatomie der Nervenschussverletzungen, Ztschr f d ges Neurol u Psychiat **29** 416-483, 1915

STRUCTURE OF THE PERINEURIUM

The classic anatomic researches of Key and Retzius [22] established the current conception of the structure of peripheral nerve These investigators named three supporting structures or sheaths besides the sheath of Schwann with which each individual fiber is provided Thus, bundles of nerve fibers are bound together by an endoneurium, and each such bundle is surrounded by an outer sheath, or perineurium which is distinct from the loose connective tissue, the epineurium, which holds several neural fasciculi together Whether the outer membrane covering the myelin belongs to the Schwann cell or is a separate condensation of inner endoneurium (sheath of Plenk and Laidlaw) is disputed [1] According to Laidlaw,[23] the endoneurial reticulum is continuous with the marginal glia where the nerve roots enter the spinal cord The perineurium is stated to be continuous with the pia-arachnoid [22]

In cross section of a nerve trunk each bundle of nerve-fibers is seen to be surrounded by its perineurial sheath, which is quite distinct from the epineurium The collagenous bundles of the latter run longitudinally in the nerve (fig 1 *B* and *C*), while the fibrils of the perineurium lie at right angles to the nerve bundle The perineurium also stains less intensely than epineurium with eosin or with phloxine The nuclei are interspersed between the collagenous bundles and are more easily studied in tangential section They are then found to be large and oval, without a nucleolus in their resting stage In maceration, they are found to be arranged in concentric layers of lamellas, separated by a collagenous fibrillar membrane, hence the old name "lamellar sheath" The perineurium is continuous with the sheaths of encapsulated end organs, such as the pacinian corpuscle, the lamellated outer structure of which is a form of specialized perineurium (Schafer [24]) The flattened "epithelioid" laminas of cells thus enclose potential spaces surrounding the nerve bunble Injection material, especially if oily in nature, can be introduced into or under the perineurium and be made to run considerable distances under slight pressure, passing into the subarachnoid space, when the injection is made into nerve roots, or into the capsules of muscle spindles, pacinian corpuscles, and so forth, when the injection is made in a peripheral direction [25]

22 Key, A, and Retzius, G Studien in der Anatomie des Nervensystems und des Bindegewebes, Stockholm, Norstedt och Soner, 1876

23 Laidlaw, G Silver Staining of the Endoneurial Fibers of the Cerebrospinal Nerves, Am J Path **6** 435-443, 1930

24 Schafer, E A Text-Book of Microscopic Anatomy, in Quain's Elements of Anatomy, London, Longmans, Green & Co, 1912, vol 2, pt 1

25. Funaoka, S, and Watanabe, M Untersuchungen uber das periphere Nervensystem, Folia anat japon **11** 37-39, 1933 Key and Retzius [22] Watanabe,

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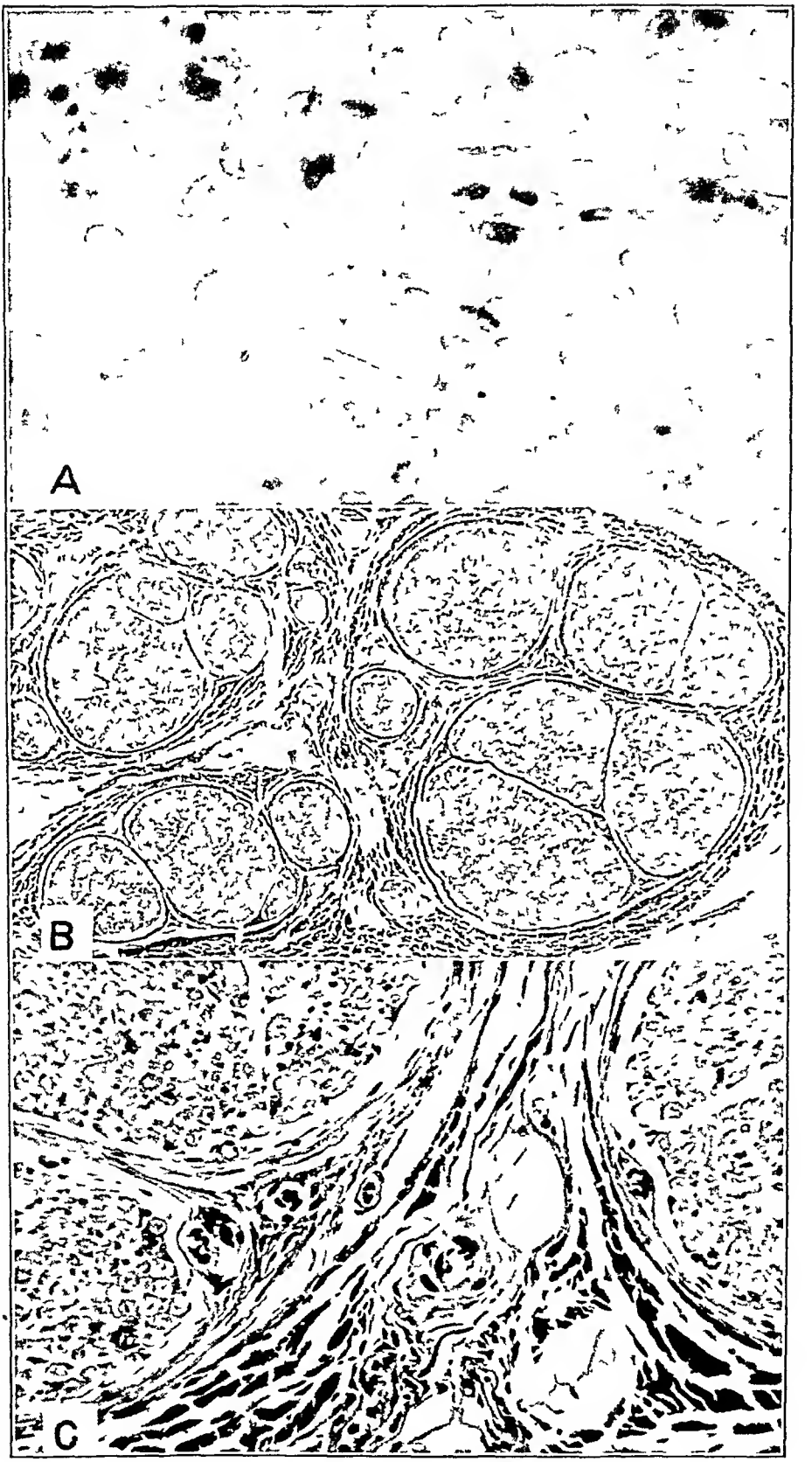

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When segments of nerve are rendered edematous, as by compression through ligature or other means or by partial ischemia,[26] fluid collects under the perineurium, separating it from the nerve bundle and the endoneurium Frequently the lamellas of the sheath then become separated by layers of fluid, and the pavement of cells is clearly defined (fig 1 *A*) The large pale nuclei closely resemble those of peritoneal mesothelium The perineurial space of digital nerves, and of nerves passing through areas of considerable movement (wrist, ulnar groove), appears regularly to contain fluid, whereas that of more proximal nerve trunks does not The perineurium forms a barrier to inflammatory processes, for my associates and I have commonly observed that the cellular reaction external to the sheath may be intensely polymorphonuclear whereas that internal to it is mononuclear This striking barrier effect is seen in the reaction to freezing in the reaction to traumatic hemorrhage of both sheaths and in certain kinds of neuritis, especially leprosy, of which I shall report elsewhere

In conditions of localized inflammatory reaction of the nerve, as in response to freezing a segment of it, edematous fluid collected under the perineurium Two special types of cell can then be seen to be shed from the perineurial lining One is the flat macrophage with eccentric, bean-shaped, pale nucleus and a central pale area in its cytoplasm, the other is a spindle-shaped fibroblast, with plump branched processes and an oval longitudinal nucleus

The perineurium, therefore, may be regarded as a natural barrier for peripheral nerve, arranged in a multilayered sheathing enclosing

M Injektionversuche in die sensiblen Nervenendapparate, Arb a d dritten Abt d anat Inst d Kaiserlich Univ Kyoto, 1935, ser A, no 4, pp 57-64

26 Denny-Brown, D, and Brenner, C Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch Neurol & Psychiat **52** 1-19 (July) 1944

EXPLANATION OF FIGURE 1

Fig 1—*A*, perineurial membrane of the sciatic nerve of the cat, edematous as a result of transitory compression 1 cm proximal to the level of section The tangential section shows the nuclear content of the lamellas between two nerve bundles, where epineurium is lacking The large pale nuclei often overlap, for they belong to different layers of the membrane ,Note also the darker, smaller, oval nuclei, sometimes pointed at one end

In this figure, and in all figures showing nerves sectioned longitudinally, the proximal part of the nerve is to the left of the figure All the tissues are from the sciatic or the ulnar nerve of the cat, with the exception of those shown in *B* and *C* of this figure

B, transverse section of the human sciatic nerve Hematoxylin and eosin stain

C, higher magnification of the upper left corner of *B*, showing the laminated perineurium and its nuclei, with small blood vessels, and the strands of epineurium in cross section, The space under the perineurium is an artefact due to shrinkage

potential spaces and loosely attached to the endoneurium by fibroblastic processes, which are prominent when edema first forms but later fall back to line a smooth-walled space Vessels entering the nerve bundle carry a sheet of perineurium into the center of the nerve bundle, where it appears to be continuous with the endoneurium The cells with large pale nuclei can be followed along the vessels within the neural bundle, where they are usually called endoneurial cells (Cajal [3]) By splitting the perineurium and grasping the nerve fibers with fine forceps through the opening, one finds that the nerve can be moved up and down within its sheath with some freedom I am not able to bring any additional evidence to the disputed question of the ectodermal or endodermal origin of the endoneurium or the perineurium and accept the general opinion that both are probably specialized fibroblastic tissues of mesodermal origin

PROCESS OF NATURAL REPAIR OF LOSS OF NERVE SUBSTANCE

Within a few hours after section of a peripheral nerve, when the severed ends are left some distance apart, exuberant sprouting of cells from each cut end begins I have already indicated the opinion of Nageotte and Cajal with regard to this process and would further cite the excellent studies of Young, Holmes and Sanders [18] on the rate of development of the cellular masses (neuroma on the central end, "schannoma" on the peripheral end) and of Ingebrightsen [27] on the phenomenon as observed in tissue culture These authors subscribed to Nageotte's view that the cells are Schwann cells, though Holmes and Young [28] (page 72) added that "the fibrous tissue of the perineurium and epineurium grows out with even greater activity than the Schwann tissue" From the observations of my associates and myself, I would add the following features First, the swellings are solid and lack the tissue spaces of the parent nerve, now distended by macrophages, with or without edematous reaction Second, the cells nearest the columns of "Schwann cells" at the cut end often lie transversely or obliquely to these, and not in direct alinement The perineurium becomes thickened at and near its cut edge, and from here rows of cells stream in line into the main mass The character of these cells does not appear to me to differ in any way from that of the cells that make up the bulk of the mass Last, when nerve fibers from the proximal stump penetrate the proximal cell mass, and, also, when they reach the distal stump, they travel on the surface of

27 Ingebrightsen, R A Contribution to the Biology of Peripheral Nerves in Transplantation II Life of Peripheral Nerves of Mammals in Plasma, J Exper Med **23** 251-264, 1916

28 Holmes, W, and Young, J Z Nerve Regeneration After Immediate and Delayed Suture, J Anat **77** 63-96, 1942

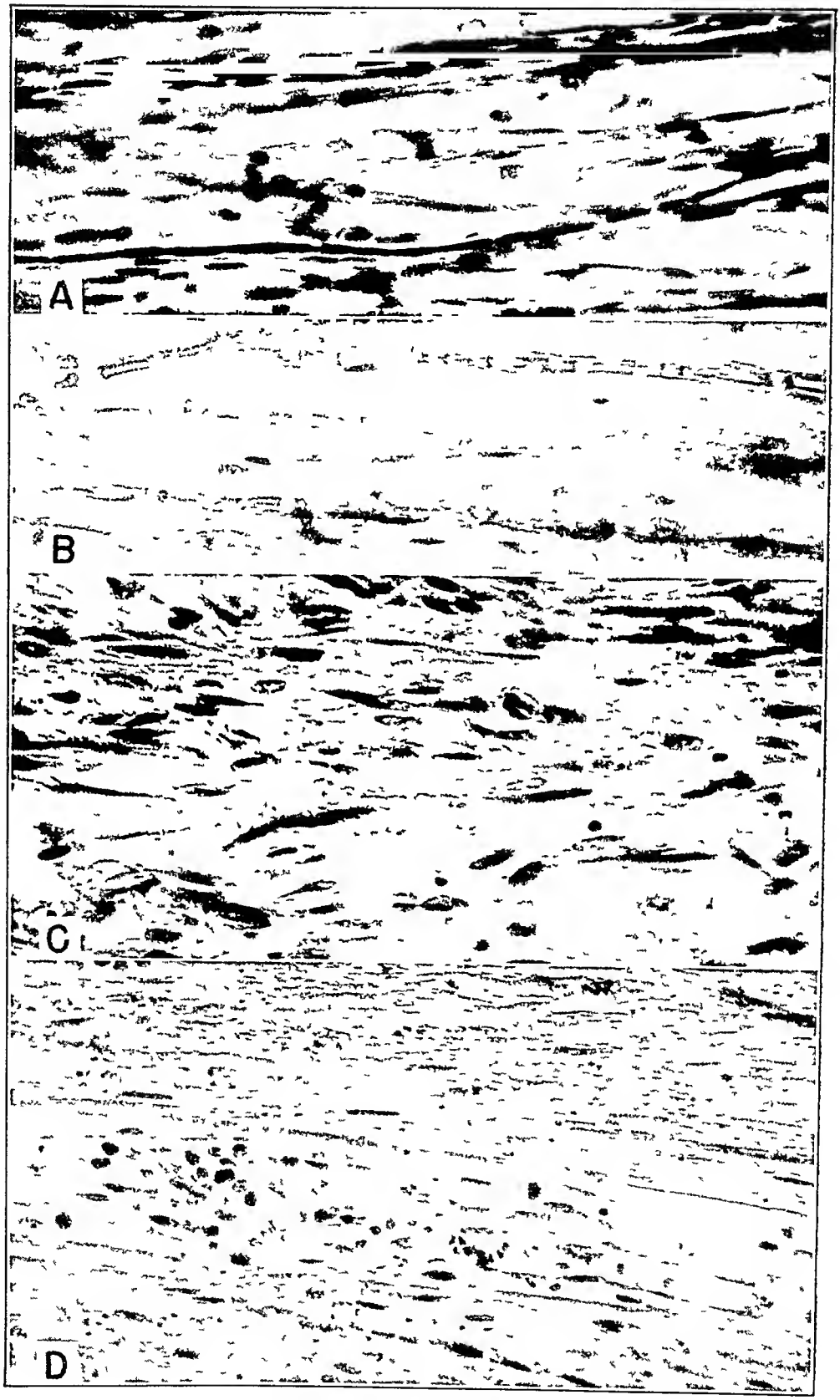
the cells, as noted by Cajal, and not in the cytoplasm, as they do in many of the Schwann bands of the peripheral nerve, and as was clearly observed by Bielschowsky and Valentin[29] in the Schwann bands after freezing and by Brenner and me[17] in the pseudoneuroma after percussion Holmes and Young[28] commented on the difficulty in distinguishing the nuclei of Schwann cells and those of fibroblasts, stressing the tendency of the former to form strands and of the latter to show irregular outline The difficulty is increased by the tendency of both nuclei to become more circular and to show a prominent nucleolus when first activated My colleagues and I have found that Mallory's phosphotungstic acid hematoxylin stain (especially Peers's[30] modification) gave fairly sharp differentiation This regularly stains the Schwann nucleus and some large connective tissue nuclei a diffuse deep blue The great increase in nuclei in cell columns of both stumps of the sectioned sciatic nerve in the cat is due to the presence of large numbers of plump oval nuclei, which either do not take the phosphotungstic acid hematoxylin stain or show only a faint blue nuclear membrane The situation is clearest in the central stump, where the nerve fibers are often separated by edema A few large pale oval nuclei of the type called "fixed connective tissue cell" by Domikow,[31] are found free in the tissue spaces, particularly near blood vessels The very small, rodlike Schwann nuclei lie closely applied to myelin or to nonmedullated nerve fibers Both these types of nuclei stand out sharply with the blue phosphotungstic acid hematoxylin stain (fig 2*B*), without any transitional elements The large numbers of plump oval nuclei with a prominent nucleolus which make up the cell columns containing regenerating nerve fibers seen in sections stained with hematoxylin and eosin or with the Nissl method (fig 2*A*) do not take the phosphotungstic acid hematoxylin stain except for blue coloration of the nuclear membrane when the stain is intense The stain colors the collagen which enmeshes these nuclei and with critical staining after fixation in Zenker's fluid the proliferating cells with unstained nuclei clearly have fibroglia, which lies within the collagen framework The nuclear membrane and nucleoli then also stain blue The cells appear to be separate and not to form a syncytium

The phosphotungstic acid hematoxylin stain further reveals that the neural scar tissue emerging from either the proximal or the distal

29 Bielschowsky, M, and Valentin, B · Die histologischen Veranderungen in durchfrorenen Nervenstrecken, J f Psychol u Neurol **29** 133-152, 1922

30 Peers, J A Modification of Mallory's Phosphotungstic Acid-Hematoxylin Stain for Formaldehyde-Fixed Tissues, Arch Path **32** 446-449 (Sept) 1941.

31 Domikow, B Beiträge zur Histologie und Histopathologie des peripheren Nerven, in von Nissl, F, and Alzheimer, A Histologie und Histopathologie, Jena, G Fischer, 1911, vol 4, pp 445-630



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stump contains few, if any, of the blue, rod-shaped nuclei until invaded by nerve fibers (fig 2 *D*) It is difficult to maintain a peripheral stump entirely free from nerve fibers, and the few nuclei found were reasonably accounted for by the few nerve fibers in the "aneuritic neuromas" The large oval "fixed connective tissue" nuclei are scattered singly or in small groups near blood vessels or in more open spaces The large numbers of plump oval nuclei which form the cell columns of the growing tissue do not take the stain, though their dark nucleoli stand out prominently (fig 2 *D*) A section stained with Masson's trichrome method reveals that all three groups are equally stained (fig 2 *C*) By these criteria, the "schwannoma" and "neuroma," before the entry of nerve fibers, are composed of cells differing from Schwann cells

Indeed, by these criteria there is a paucity of Schwann nuclei at both the central and the peripheral cut end of nerve for the first 3 to 5 mm (fig 3 *A* and *B*) The characteristic thread of cytoplasm of each Schwann cell in the bands of Bungner of the main distal degenerated portion of the nerve is found to shrink progressively as one passes from the main trunk of the distal piece of peripheral nerve into the first 5 mm of the peripheral stump The few remaining rod-shaped cells in the stump itself did not have processes (fig 3 *B*) In the same region of transition, more and more plump nuclei staining poorly with phosphotungstic acid hematoxylin occupy the columns In critical staining the nuclear membrane takes the stain, and fibroglia is present (fig 3 *D*) Some of the nuclei are narrow, but these have sharp ends Either the Schwann nucleus undergoes complete metamorphosis or it is replaced My associates and I have considered the possibility that the staining characteristics alter with regeneration A study of scars of different ages revealed that the fresh nuclei shaped like narrow, blunt rods and showing frequent mitoses enter the scar only when accompanying the regenerating nerve fibers and follow the course of such fibers In this migration the Schwann nuclei retain

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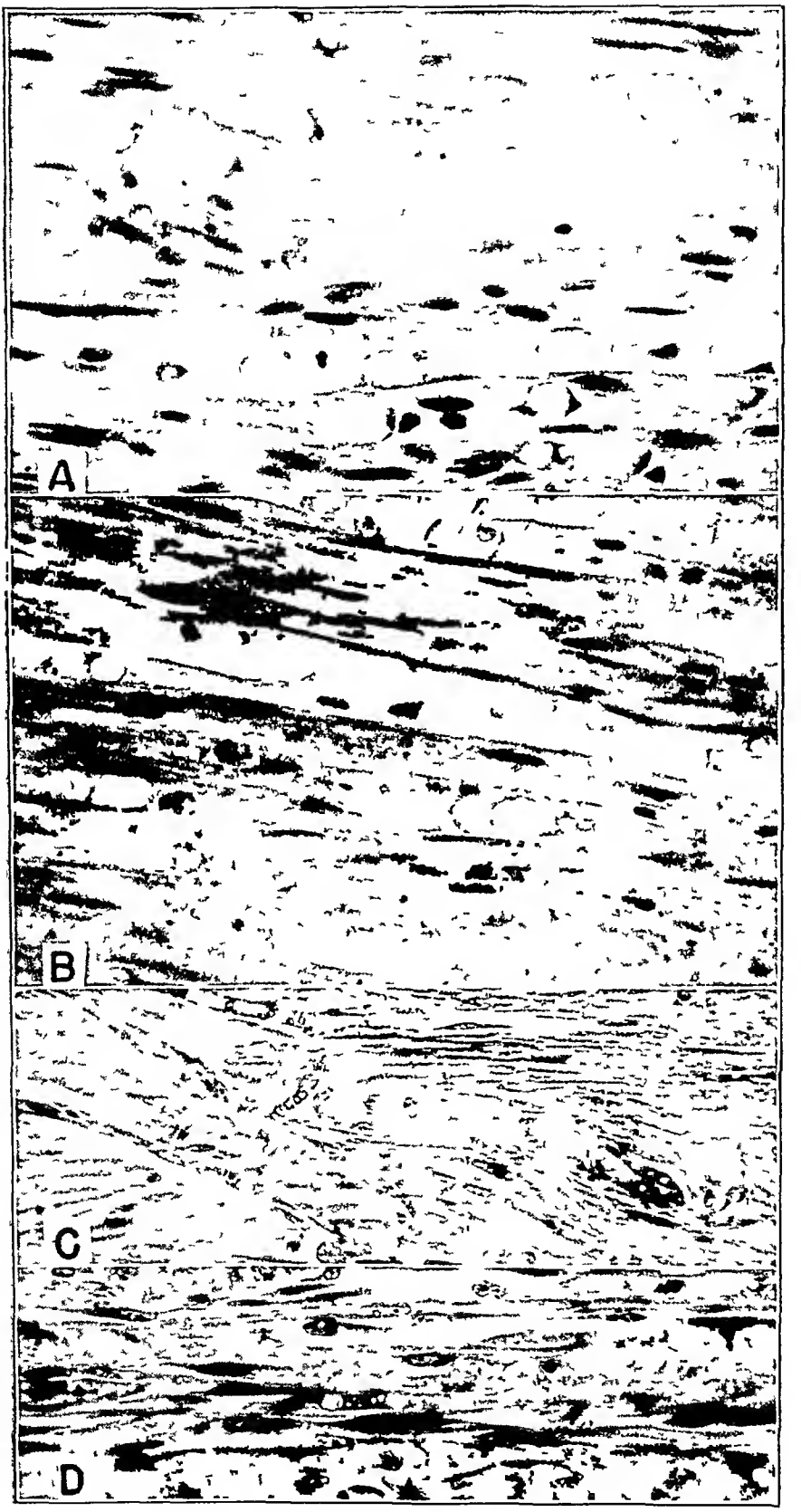
EXPLANATION OF FIGURE 2

Fig 2—*A*, section from the edematous region of the central stump of a sciatic nerve divided seventy-five days before Fixation in solution of formaldehyde U S P , Gros-Bielschowsky method, counterstained with hematoxylin and eosin *B*, section from the same region as that shown in *A*, stained with phosphotungstic acid hematoxylin (Peers's modification) *C*, section from the scar tissue bridging the two stumps twenty-one days after section of the sciatic nerve Note the two Schwann nuclei in the upper central field Fixation in Zenker fluid, Masson's trichrome method *D*, section from the same region as that shown in *C*, stained with phosphotungstic acid hematoxylin A small vessel with mononuclear cells occupies the lower central field Note the three Schwann nuclei above this The numerous black dots are nucleoli of unstained fibroblastic nuclei The nuclear membranes and the fibroglia are not stained. Note the two Schwann nuclei lying above the vessel and histiocytes



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their peculiarity of staining and form The oblique separation of freshly divided nuclei is especially characteristic Further, when myelination begins, most such nuclei are found embedded in a myelin segment We have not found such Schwann nuclei closely embedded in collagen

The nuclei of the cells composing the "junctional tissue" or scar are variable in size and shape, being more sharp pointed and oat shaped when the linear arrangement and collagen lines appear to indicate tension and more plump and oval when they are lying free in a tissue space They are commonly rounded at one end and slightly sharper at the other One or two nucleoli are prominent In view of the intense proliferation both within the nerve stumps and in the scar, it is suprising to find little evident mitosis Many of the oval nuclei show a prominent nucleolus at either pole with a constriction in the middle, and this has undoubtedly led many authors to consider that these cells divide amitotically [12] Careful inspection of a phosphotungstic acid hematoxylin preparation reveals, however, that a typical metaphase does occur, though the clusters of chromosomes are very small, and at first sight look like ragged nucleoli They are about half the size of the spindle of the smallest Schwann cells In the more common prophase the nucleus is tigroid in appearance

These nuclei can be traced back from the scar into the cell columns of the nerve stumps, where they are in active division, as indicated by Masson [62] They can, however, be traced farther into the main trunk of the degenerated peripheral segment, where, in much smaller numbers, they are found in characteristic form, lying on the surface of the columns of Schwann cells (fig 3 *D*) The nucleus of the resting cell frequently stains a light diffuse blue with phosphotungstic acid hematoxylin and may have no nucleolus, but is still much paler than the

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EXPLANATION OF FIGURE 3

Fig 3.—*A*, section from the distal stump of a divided sciatic nerve twenty-one days after section, 2 mm from the level of section Note the large, pale, oval or circular nuclei and the numerous darker, smaller oval or pointed nuclei accompanying the collagenous bands Some rod-shaped Schwann nuclei with blunt ends are seen near the lower left and the upper right corner Fixation in Zenker fluid, Masson trichrome stain

B, tissue from a section near that shown in *A*, stained with phosphotungstic acid hematoxylin The dark, diffusely stained nuclei in the cell columns belong to Schwann cells The irregular nuclei belong to phagocytes The fibroblastic nuclei are represented only by the nucleolus and a faint outline

C, junctional tissue between the nerve ends of the sciatic nerve, frozen for three and a half minutes and sectioned in the frozen segment sixteen days earlier Most of the cells show fibroglia None of the nuclei stain diffusely Fixation in Zenker fluid, phosphotungstic acid hematoxylin stain

D, critical staining of distal nerve stump, 3 mm from the end Two Schwann cells lie in the lower middle of the figure The fibroblasts have well developed fibroglia processes, which branch in clefts between collagen fibers Fixation in Zenker fluid, paraffin embedding, phosphotungstic acid hematoxylin stain

Schwann nucleus The plump oval nucleus often lies slightly oblique to the longitudinally oriented Schwann bands Mitosis is common These cells are here identical with those which Dominkow [31] called endoneurial cells Amitotic division was also noted by Dominkow, but we found the same small mitotic spindles These elements differ from the large flat cells with broad nuclei (endoneurial cells of Cajal, fixed connective tissue cells of Dominkow) lying near blood vessels in being more oval, sometimes even sharp at the end, and having two plump stems of cytoplasm Brenner and I [18] noted that they proliferated rapidly and became wrapped around nerve fibers injured by percussion

Observation of the selective necrosis of nerve induced by freezing nerve [32] indicated a further possible means of separating the contributions made by Schwann cells and perineurium to the scar, for Schwann cells were found to be extremely sensitive to freezing A segment of sciatic nerve in the cat was frozen hard for three and a half minutes, thawed with warm saline solution and then sectioned in the middle of the previously frozen segment and left for two weeks The two nerve ends were found to be joined by the usual fibrous band at the end of this period Section showed that at the end of the stumps no Schwann cells survived, though abundant phagocytes filled with fat poured from the cut face of the nerve The epineurium had undergone proliferation and contributed fibroblasts to the scar The greater part of the scar, however, was made up of columns of cells streaming from thickened perineurium directly into the tensile scar and holding the nerve ends together Endoneurial cells of identical kind also contributed A diffuse brown collagen surrounded both the perineurial and the endoneurial cells and their derivative tissues, differing from the red strands which accompanied epineurial fibroblasts All these cells had fibroglia, and those derived from perineurium and endoneurium had nuclei which failed to stain with phosphotungstic acid hematoxylin or showed only the nuclear membrane and the nucleolus (fig 3 *C*) The scar thus formed appeared to be identical with that normally found

The formation of increased numbers of both large oval and moderate-sized plump nuclei could be traced from perineurium, as well as from residual strands of endoneurium Inspection of flat preparations of perineurium reveals that they are there also normally present in small numbers (fig 1 *A*), preserving the same differences which distinguish them in endoneurium One may conclude, therefore, that the cellular proliferation in nerve following injury and leading to scar formation is related to a type of cell present in the perineurium and

32 Denny-Brown, D , Adams, R D , Brenner, C, and Doherty, M M The Pathology of Injury to Nerve Induced by Cold, J Neuropath & Exper Neurol, to be published

endoneurium which has the characteristics of a fibroblast but which differs from the epineurial fibroblast in at least two respects, namely, a tendency to form a diffuse type of collagen and absence of diffuse nuclear staining with phosphotungstic acid hematoxylin The cells also tend to become oriented in parallel rows, especially when under tension They appear to be identical with the palisaded perineurial fibroblasts of Mallory [33]

REGENERATION OF NERVE WITHIN INTACT PERINEURIUM

As a corollary to the conclusion reached earlier, it was logical next to inquire as to the fate of a nerve sectioned and left within its natural perineurial sheath The ulnar nerve, being in the greater part of its humeral segment a single homogeneous fasciculus in the cat, was selected The nerve was exposed, drawn taut and a longitudinal incision 5 to

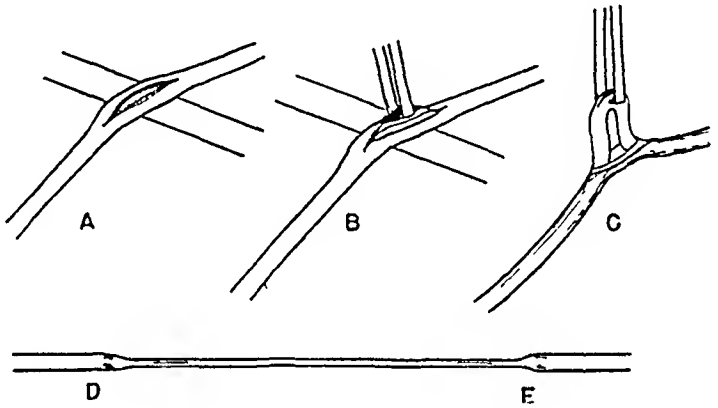
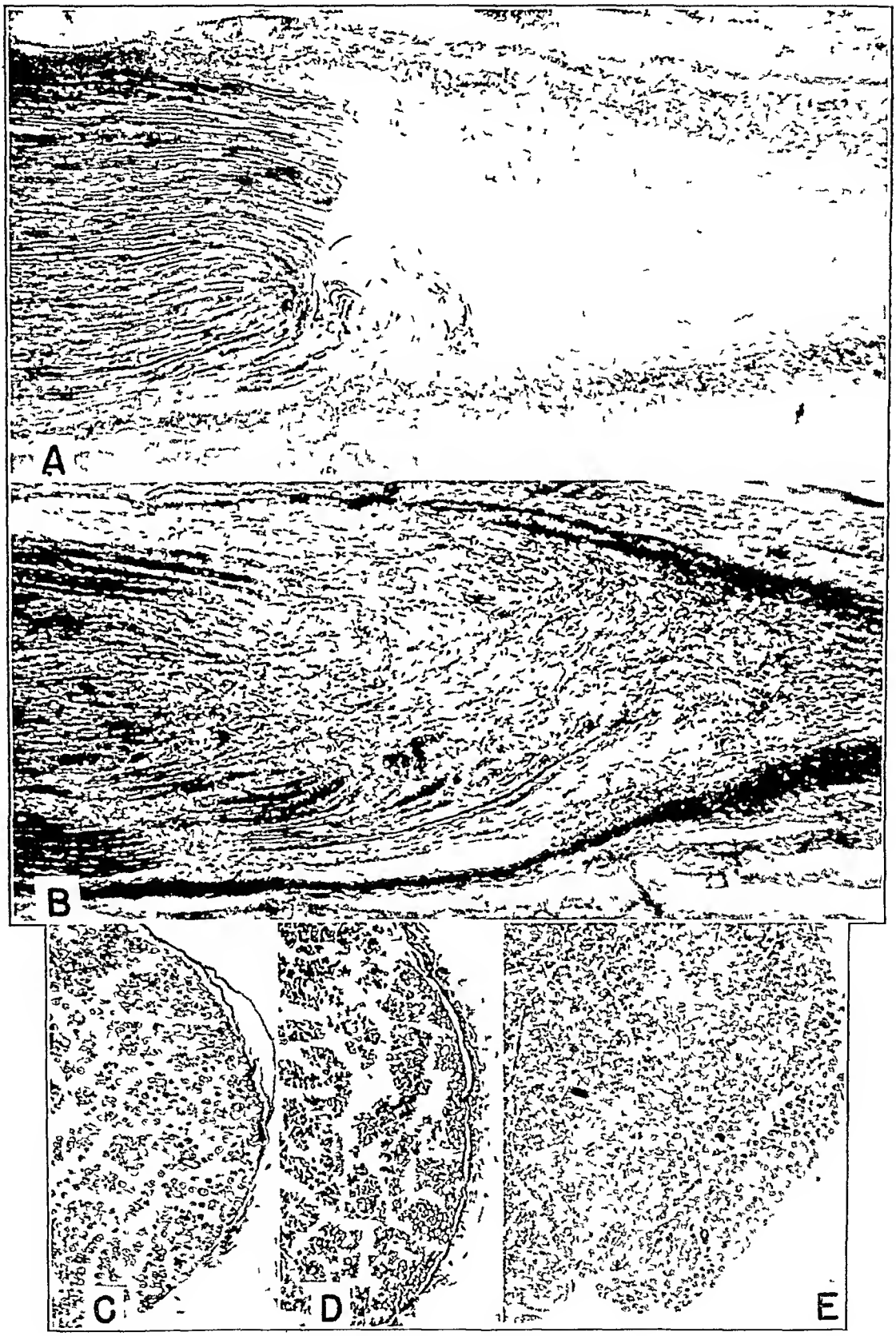


Fig 4—Method of extraction of the contents of the perineurial sheath described in the text

7 mm in length made into the fasciculus in its distal third (fig 4 *A*) The edges of the incision gaped apart, and the cut surfaces of the nerve fibers were grasped in a fine-toothed forceps, care being taken to avoid the cut edges of the perineurium (fig 4 *B*) By traction the nerve bundle was herniated through the slit in the perineurium, which was peeled back gently A firmer grip was then taken of the whole bundle (fig 4 *C*) The loop of nerve fibers was then cut at its distal end A similar incision was made 2 to 3 cm proximally, and the loop of nerve pulled out was sectioned at its proximal end after pulling back the perineurium as far as possible By gentle traction on the upper loop the intervening segment of nerve fibers was now pulled out of the perineurium, leaving a membranous tube with two slit-shaped incisions (fig 4 *D* and *E*) In some experiments three incisions were made, the nerve being withdrawn in two segments, so as to avoid undue trac-

33 Mallory, F B The Type Cell of the So-Called Dural Endothelioma, J M Research **41** 349-364, 1919-1920



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tion by pulling a long piece from one end It is important that the perineurium should be handled as little as possible and not ruptured In large nerves with more epineurium it is necessary to be sure that nerve fibers deep in the incision are alone caught by the forceps and that the nerve bundle as it is pulled forth sheds all the perineurial sheath in the first pull, so that thereafter it emerges smooth and glistening, without any trace of blood vessels or fibrous tags Transverse section of this piece of nerve thus pulled out usually showed one or two adherent lamellas (fig 5 *C*) and was sometimes completely denuded (fig 5 *E*) If the nerve is pulled too hard or is insufficiently separated, the whole perineurium, with tags of epineurium, may be removed (fig 5 *D*) Only by such section can one be sure that the perineurium itself is not also dragged forth

The condition of the central stump, surrounded by the intact perineurial tube, twelve hours after the operation is shown in figure 5 *A*, in which the retraction of the nerve fibers, the ends of which had fragmented, will be seen The perineurial sheath had frayed into separate laminas and, with the epineurium, was the seat of a mild inflammatory reaction There was a very slight hemorrhage A section of the center of the perineurial tube after the same period showed that the walls had collapsed together, obliterating the central lumen The perineurial cells and their lamellas had already swollen to form a laminated solid band

The procedure just outlined was carried out at open operation with the animal under deep pentobarbital anesthesia, leaving a 3 cm gap in the nerve with intact perineurium, and as a control the left ulnar nerve was excised so as to leave a 3 cm gap between the cut ends After an interval of twenty-eight days the nerves were exposed with the animal under pentobarbital anesthesia Electrical stimulation above and below the gap elicited no movement on either side Whereas the nerve ends on the left side (total excision) now each presented a large neuroma, connected by a fibrous band densely adherent to muscular and other neighboring tissues, the nerve on the right side remained thin and as freely movable as a normal ulnar nerve There was a slight enlargement of the former proximal nerve fasciculus, which tapered down to a fibrous cord 1 cm long, and distally this

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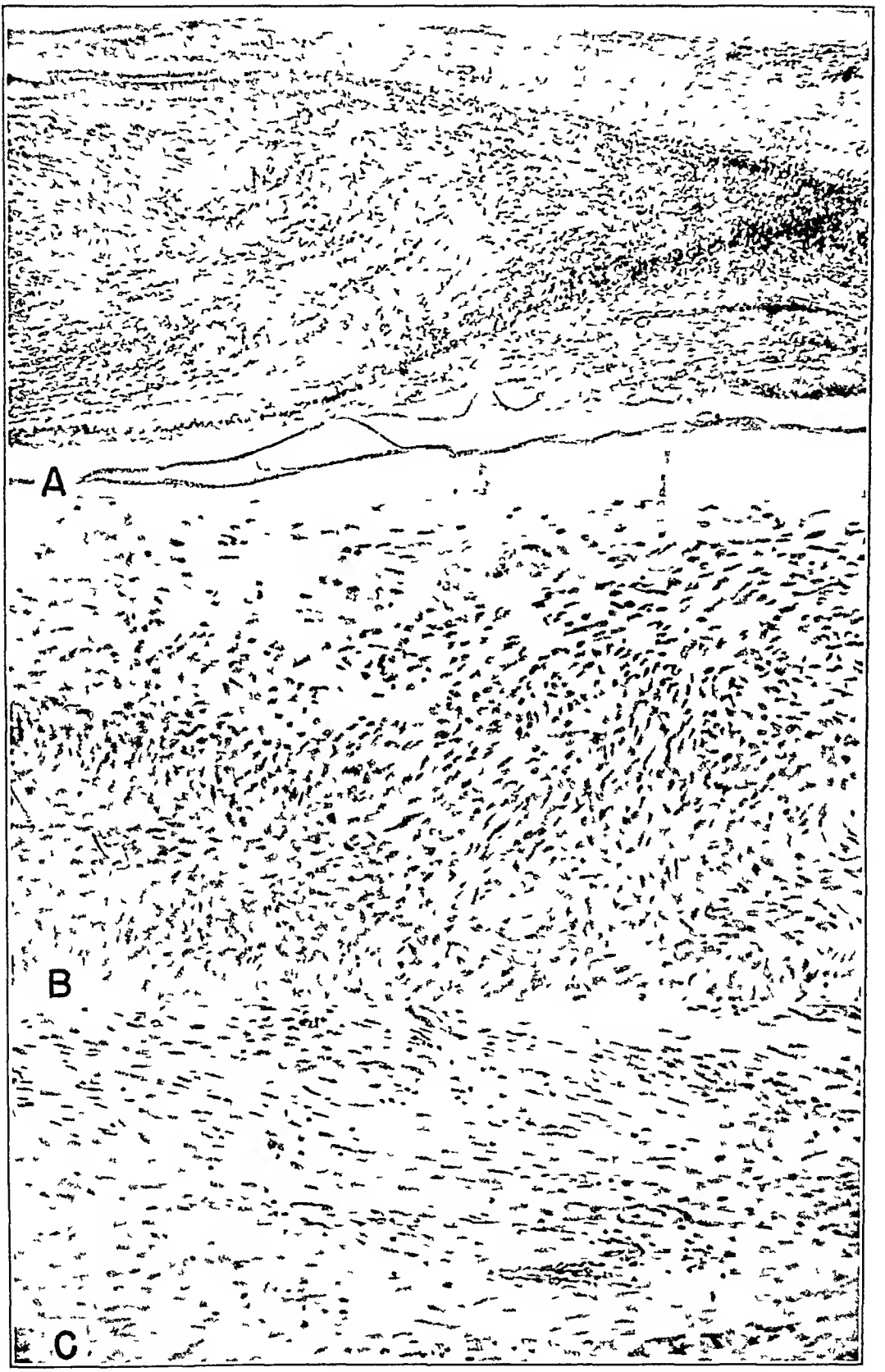
EXPLANATION OF FIGURE 5

Fig 5—*A*, proximal stump of ulnar nerve twelve hours after subperineurial excision Gros-Bielschowsky method, counterstained with hematoxylin and eosin

B, proximal stump of ulnar nerve, twenty-eight days after subperineurial excision, Gros-Bielschowsky method, cresyl violet stain

C and *D*, sections of avulsed portion of the ulnar nerve from various experiments mentioned in the text Hematoxylin and eosin stain



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tapered gradually to the normal diameter of the nerve without distal enlargement Section of the proximal extremity of the perineurial tube revealed that the slight enlargement was caused by dilatation of the tissue spaces of the nerve at and just beyond the original point of section (fig 5 *B*) The perineurial sheath had formed a cone, enclosing growing nerve fibers This edematous central nerve end showed intense proliferation of endoneurial fibroblastic nuclei with elongation of axis-cylinders, many of which crossed and recrossed and a few of which had just penetrated the tip of the wedge These fibers were accompanied with moderately numerous Schwann nuclei, resembling the condition shown in figure 2 *A* There was intense cellular proliferation at the distal extremity of the perineurial cone (fig 6 *A*), which lay 5 5 mm from the level of original section, and large numbers of cells with pale oval nuclei and branched, pale cytoplasm in a loose spongy tissue filled the center of the conductor beyond (fig 6 *B*), becoming distally more sparse (fig 6 *C*) but extending as a cellular cord to meet a cone-shaped extension of perineurial cells extending medially for 3 5 mm from the distal stump (fig 7 *A*) Loose cellular fibroblastic laminas extended from the central cord to the surface, where more dense epineurial strands formed an outer layer (fig 6 *B*) Small blood vessels permeated the whole tissue

There was no difference between the nuclei of the distal cell mass and those which extended distally from the central perineurial cone In sections stained for collagen with Mallory's phosphotungstic acid hematoxylin (figs 7 *B* and *C*) these cells were found to have the staining characteristic of those we have identified as perineurial and endoneurial fibroblasts in neural scars In addition, it was seen that, whereas both cellular cones were lightly and diffusely collagenized, funnel-shaped collagenous septums appeared to spring from the walls of the tube as lamellar bands and strands over the intermediate section In places the central columns of cells were subdivided longitudinally by such a partition In addition, a collagenous deposit had extended into the first 2 mm of the distal stump, as is usual in all nerve stumps

At the four week stage, therefore, the situation represented a collapse of the original perineurial tube with proximal reopening by an active growth tip of nerve fibers covered by Schwann cells and having the

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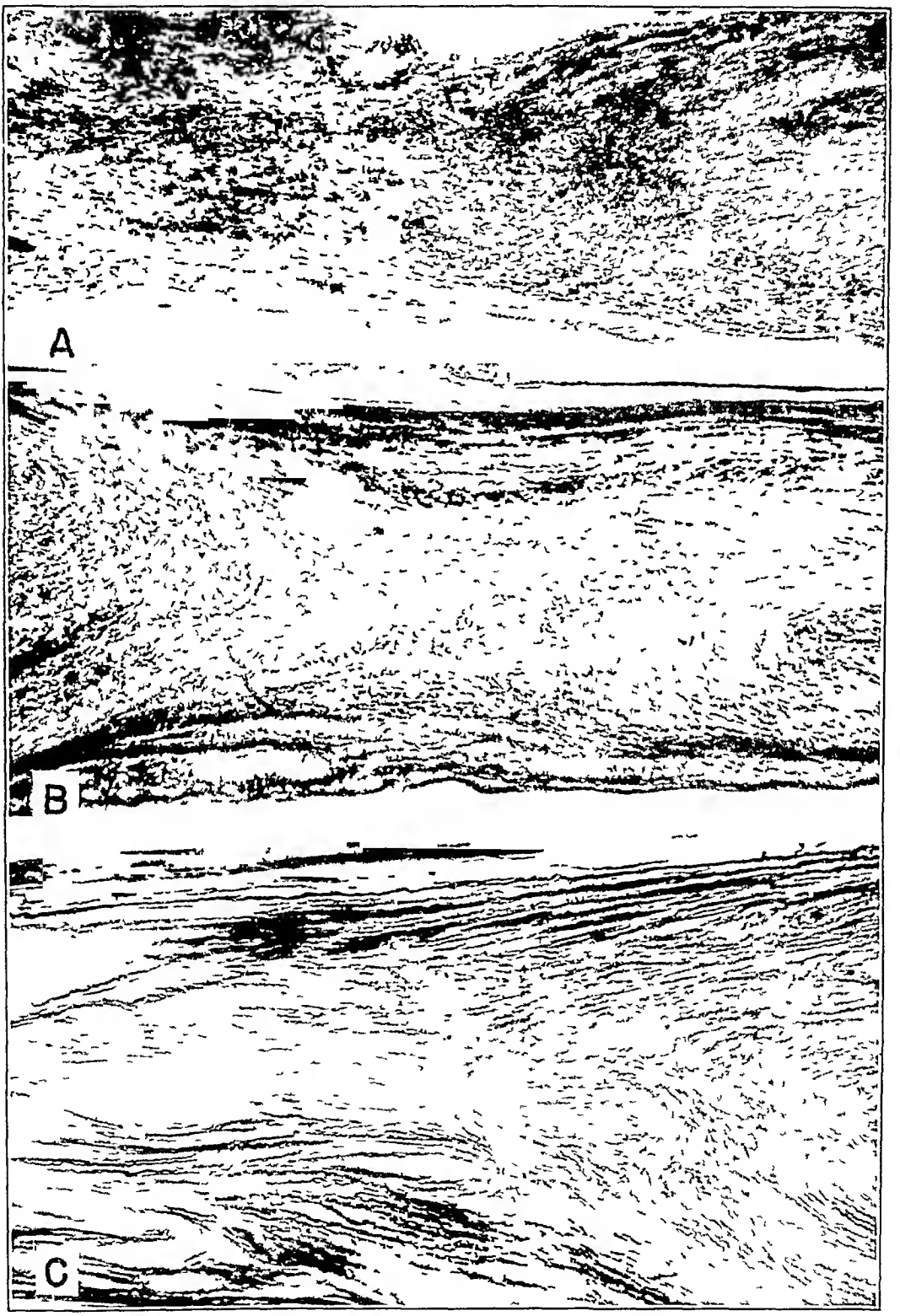
EXPLANATION OF FIGURE 6

Fig 6—Proximal stump of ulnar nerve, as shown in figure 5 *B*, twenty-eight days after subperineurial excision Hematoxylin-eosin stain

B, higher magnification of the cellular apex to the right of the point from which *A* was taken

C, core of the perineurial connection about 1 cm distal to the point from which *B* was taken



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appearance of a fluid wedge There was much spiraling of the nerve fibers in the edema proximal to this wedge but no true neuroma formation The cone of the connecting scar appeared to consist of activated fibroblasts without Schwann cells There were few Schwann cells in the first 2 mm of the peripheral stump

LONG TERM SURVIVAL AFTER SUBPERINEURIAL EXCISION OF ULNAR NERVE

In another experiment, the fibers of the right ulnar nerve were similarly excised for 3 cm , leaving the perineurium The left ulnar nerve was sectioned in three places, leaving two pieces 1 1 and 1 2 cm long, respectively, in a gap of 3 cm There were thus three gaps of 0 5, 0 1 and 0 1 cm , respectively, in the control nerve After an interval of ninety-nine days the nerves were explored with the animal under anesthesia The nerve on the left (control) side presented three large neuromas, which with the intervening pieces of nerve were densely adherent to the neighboring vessels and muscles On the right side the ulnar nerve appeared thin for about 2 cm , and two slight enlargements marked the site of former avulsion of its contents (fig 11 *A*) No adhesions of any kind were present Electrical stimulation of the control ulnar nerve above the triple lesion excited a weak (25 per cent) flexion of the wrist with weak protrusion of the radial claw Stimulation of the right ulnar nerve excited moderate (50 per cent) flexion of the wrist, with strong protrusion of the radial claw

Sections of the left ulnar nerve showed the appearance characteristic of neuromatous neural scars The right ulnar nerve was sectioned transversely at the junction of the upper and the middle third and of the middle and the lower third and was stained with osmic acid This preparation showed one small medullated branch surrounded by perineurial sheaths at each level This appeared to be a small subsidiary bundle missed in the original "pulling" of the nerve The remainder of the section was fibrous, with numerous scattered nerve bundles, each in a stage of advanced myelination

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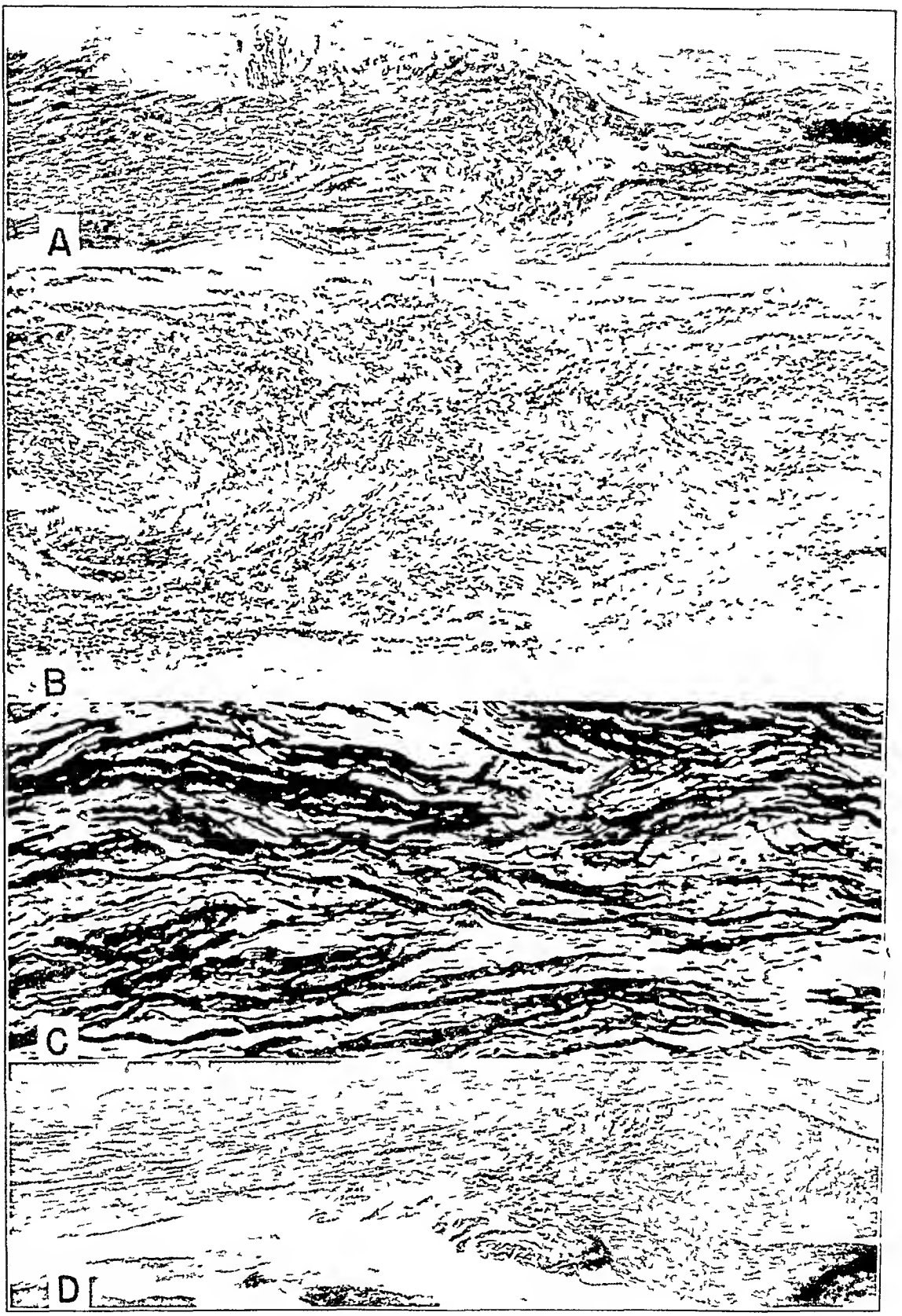
EXPLANATION OF FIGURE 7

Fig 7—*A*, section from the same experiment as the sections in figure 6, the distal stump of the nerve being shown on the right with dense cellular mass extending medially as a cone into the perineurium Cresyl violet stain

B, section from the same experiment, the proximal cellular cone being stained with phosphotungstic acid hematoxylin (Peers's modification) The tip of the cone lies at the junction of the right and the middle third No Schwann nuclei lie distal to this

C, section from the same experiment, showing the distal cone stained with phosphotungstic acid hematoxylin



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Longitudinal sections showed that nerve fibers had advanced through the entire length of the area of excision (fig 8) In the region of the original proximal section, Perroncito spirals were frequent but of loose structure and passed by a heavy regeneration of nerve fibers, which coursed as several bundles 3 5 mm after leaving a proximal cone (fig 8 *A*) They then coursed as one bundle for 2 mm At this level some septal partition appeared The nerve then continued as separate bundles partitioned by thin septums until, 4 mm from the distal nerve end, still recognizable by its fatty phagocytes, they met the apex of the solid mass of cells projecting medially from the peripheral segment (fig 8 *D*) At this point the axis-cylinders continued their peripheral course, running separately in the interstices between the fibroblastic cells until the cone of the peripheral stump was attained The nerve fibers took oblique and interlwining courses throughout the long passage (fig 8 *C*), but none was seen to turn back and no neuromatous confusion of direction was observed

The distal cone was asymmetric (fig 8 *D*), having grown laterally to one side in a neuromatous bulge, which was attributed to part of the entire perineurium having been withdrawn in the original pulling and being present with the avulsed nerve at this end (fig 5 *D*) The bundles of nerve fibers had, however, by-passed this region and made satisfactory connection Many fibers had myelinated throughout their length, and many more had matured in the peripheral nerve than in the control limb, but the structure of the nerve which had grown through the perineurial tube was not complete In the most peripheral part of the former tube and in the distal nerve segment great numbers of fine-beaded regenerating fibers were present, hence, much more complete regeneration might have occurred had the period been longer The architecture of the new nerve differed from the normal in that perineurium and endoneurium were as yet undefined except for some superficial condensation of fibrous layers in the most proximal portion (fig 8 *B*) In preparations stained with phosphotungstic acid hematoxylin the new nerve throughout its length showed collagen in the

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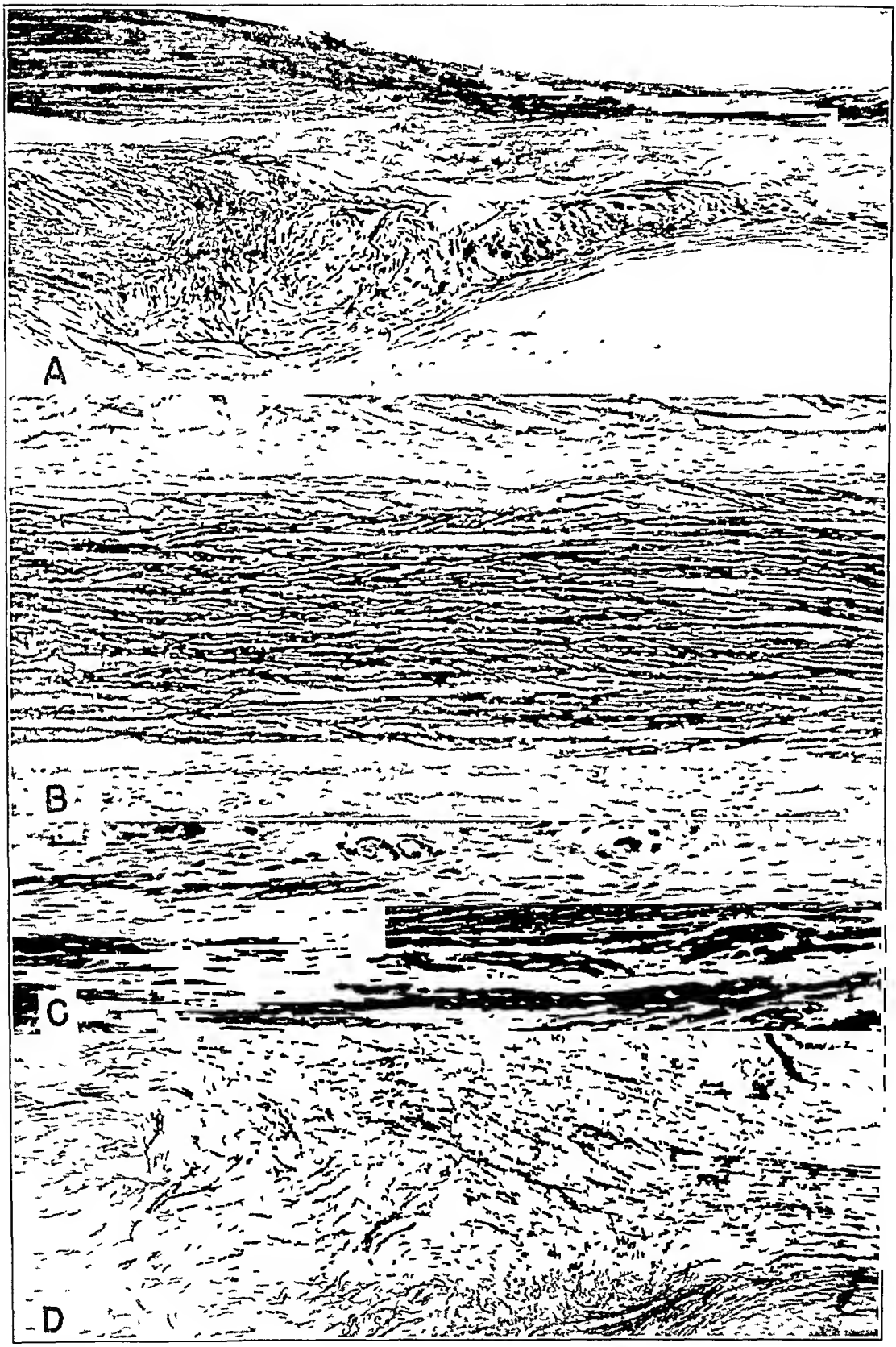
EXPLANATION OF FIGURE 8

Fig 8—*A*, proximal stump of ulnar nerve, ninety-nine days after subperineurial excision The original stump lies near the left border, where several Perroncito spirals are seen as dark bodies among the axis-cylinders The new nerve passes to the right Gros-Bielschowsky method, cresyl violet stain

B, cellular detail of the newly formed nerve 3 cm distal to the point at which *A* was taken

C, higher magnification of field in *A*, showing axis-cylinders to the extreme right of *A*

D, distal stump, showing the distal cell mass cut somewhat obliquely Gros-Bielschowsky and cresyl violet stain



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form of fine longitudinal bundles All the nerve fibers had scattered Schwann cells, but the main bulk of the cellular columns was made up of the pale oval fibroblastic cell of endoneurial or perineurial type (fig 8 *B*)

SUBPERINEURIAL EXCISIONS OF PERONEAL NERVE

In 3 other long term experiments, the sciatic nerve was exposed at operation and the popliteal division excised for varying distances The peroneal division was then treated, as was the ulnar nerve in the first experiments Thus, in the same wound, subperineurial excision of peroneal nerve was tested against total excision of popliteal nerve The epineurium and the perineurial tube of the peroneal nerve prevented further separation of the two ends of the popliteal nerve

In such an experiment, 3 4 cm of popliteal nerve was excised completely, and 3 2 cm of peroneal nerve was pulled from two openings in its sheath, leaving a gap of 3 2 cm between the ends Recovery of some dorsiflexion of the foot was observed clinically on the ninety-third day Exploration on the one hundred and sixth day revealed that electrical stimulation of the peroneal nerve above the lesion elicited an estimated 30 per cent dorsiflexion of the foot and spreading of the toes and that stimulation of the popliteal nerve produced only a faint flicker in the soleus muscle, without movement of the foot There was no trace of cross connection A large neuroma densely adherent to surrounding muscle and areolar tissue marked the situation of the former nerve ends, and a new nerve connected these Transverse section of the nerve halfway between the neuromas showed two types of regeneration—the one in small bundles of nerve fibers lying in the fibrous tissue and the other in one homogeneous bundle, already showing evidence of independent perineurium (fig 10 *A*) There was no difference in the average size of fibers between these two groups Longitudinal section of the proximal neuroma showed that it was almost wholly

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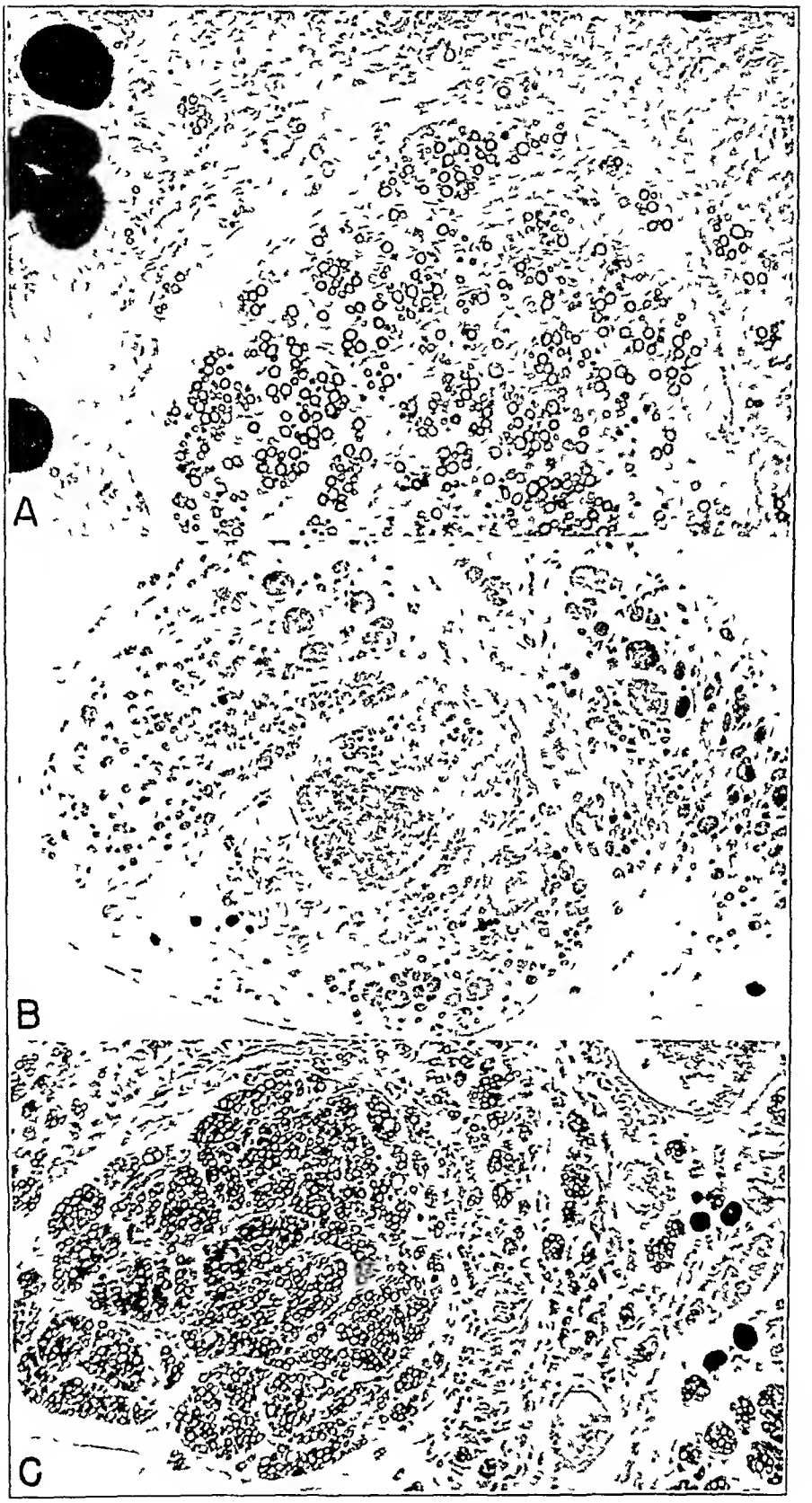
Explanation of Figure 9

Fig 9—*A*, sciatic nerve, with the peroneal nerve above and the popliteal nerve below Gros-Bielschowsky method, cresyl violet stain Both views had been resected from the same level one hundred and six days earlier, the peroneal nerve subperineurially and the popliteal nerve entire New nerve appears above and a neuroma below

B, higher magnification of the new peroneal nerve taken just distal to the right of *A*

C, section similar to *B*, showing condensation of pale nuclei at the edge of the nerve

D, distal stump of peroneal nerve shown in *A*, showing junction of fibers through the distal cell mass, the diameter of which is about 50 per cent greater than the full diameter of the peroneal trunk, shown here Section at a superficial level



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composed of a terminal neuroma on the popliteal division (fig 9 *A*), from which the small separate fiber bundles in the epineurium were derived The peroneal nerve had reproduced a nerve slightly less than its own diameter, and this was traced directly to the peripheral peroneal nerve trunk, into which large numbers of fibers were entering (fig 9 *D*) In spite of the absence of any well defined sheath, the straying bundles from the popliteal nerve were not observed to enter the sheath of the peroneal nerve at any part of its course, nor did any of the latter stray into the former group The new peroneal nerve is shown in figure 9 *B* It traveled as a compact single bundle for 2 3 cm and thereafter showed several collagenous subdivisions At its margin a condensation of flat, pale fibroblastic nuclei represented the new perineurium (fig 9 *C*) The bundle contained more collagenous material than normal nerve, and this was arranged in longitudinal strands The Schwann cells and longitudinal vessels were of normal appearance except that absolute parallelism of fibers was not attained

There were no spirals or reverse turns The cellular growth from the distal peroneal stump tapered 5 5 mm proximally where it merged imperceptibly with the cellular cone of the "tube" There was a slight bulge just proximal to the distal level of section, and here the nerve fibers became tortuous in their course through the cell mass There did not appear to be any loss of fibers, however, and the peripheral nerve was well filled (fig 9 *D*)

In a second experiment, the time interval allowed (eighty-eight days) was too short to permit return of conduction across the gaps (4 5 cm) of either the peroneal or the popliteal division of the nerve Sections, however, revealed a situation identical with that described in the preceding paragraph The peroneal bundle traveled as a large single band (fig 10 *B* and *C*), surrounded by small bundles of popliteal fibers, which frequently turned back Fibrils had reached the peripheral peroneal stump in large numbers, but few had matured at this level There was no formation of neuroma at either end, though such masses were prominent in the popliteal division No exchange of fibers had taken place In another experiment, in which there were 4 3 cm

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EXPLANATION OF FIGURE 10

Fig 10.—*A*, transverse section of the new peroneal nerve shown in figure 9 *B*, halfway between the two stumps Note the stray bundles of popliteal nerve in the epineurium Osmic acid stain

B, transverse section of the whole sciatic nerve halfway between the two stumps after total excision of the popliteal nerve, and subperineurial resection of the peroneal nerve ninety-six days earlier Osmic acid stain

C, higher magnification of the new peroneal nerve shown in the center of *B*

of total excision of the popliteal nerve and 5.2 cm. of subperineurial excision of the peroneal nerve and the animal was killed at the end of ninety-six days, faint contraction occurred in the soleus group on stimulation of popliteal nerve above the lesion and no response was elicited from the peroneal nerve. Sections showed a few fibrils entering the peripheral peroneal stump, having just traversed the distal perineurial and endoneurial proliferation, which had formed a moderate distal enlargement. In this case, however, a neuroma had formed at the middle of the gap, and this was found to be due to the rupture and coiling of a nerve branch, which had thus channeled most of the peroneal fibers into a cul-de-sac. Evidently, the initial extraction of nerve contents had taken the perineurium, as well as the nerve bundle, from the lower slit and only the nerve bundle from the upper. Examination of a section of the pulled nerve indicated that only one layer of perineurium was attached to it, but care had not been taken to section either end of the pulled piece.

It is to be concluded, therefore, that excision of a nerve trunk within its perineurium is followed by regeneration of the nerve bundle until functional connection with the distal segment is reached. The nerve was reconstituted over a 3 cm. gap, with a 30 to 50 per cent return of function after approximately one hundred days and with fiber continuity beginning to be established over 4.5 and 5.2 cm. gaps in eighty-eight and ninety-six days, respectively. The control experiments indicate that nerve fibers growing freely across total excisions of nerve, with such framework as the epineurium of a neighboring bundle can provide, can establish contact with the peripheral segment at a similar rate but with such a degree of fiber loss by dispersion that resulting recovery of function is greatly impaired in the larger gaps. Longitudinal section of the epineurium gave frequent evidence of reversal of direction of such fibers growing in simple fibrous tissue.

The presence of a perineurial sheath prevented the formation of both central and peripheral neuromas. A slight swelling of the proximal segment in the early stages represented a coiling of the growing nerve fibers and Schwann sheaths behind the expanding wedge of proximal stump. This phenomenon, with its enclosed Perroncito spirals, later tended to disappear. The perineurial meshwork formed by the collapse of the original perineurial tube was slowly reformed into a laminated sheath for the growing nerve, which eventually establishes contact with the peripheral segment. The latter contributed to the process only by the formation of a conical cellular mass which received and transmitted the nerve fibers that reached it. The central stump provided the reformed nerve with endoneurium and vessels. Some small vessels entered from the walls of the original tube. There appears to be no

limit to the size of the reformed nerve, for the perineurium is expanded by its contents and excites no external fibrosis or adhesions and the prevailing pattern of fibrous tissue is longitudinal rather than transverse

In this process of reformation of nerve the growing nerve fibers brought Schwann cells with them The ultimate growing tips of the fibers appeared as chains of beads connected by extremely fine threads These lay on the surface of the fibroblast cells, being always separated from the nucleus by a space (fig 15 *C*), as maintained by Cajal The growing tip of the nerve fiber was seen as the last of a series of very fine beads connected by a faint thread No accumulation of Schwann nuclei was found at any one point, and their distribution was sparse, though fairly even throughout the bundles of growing fibers except in the first millimeter of growth and distal to that point On all fibers which could be traced any distance from the growing tip, the first Schwann cell was encountered about 0 25 mm proximal from the tip Mitosis of the last nucleus was not seen in these specimens, though it was frequent in the general region of growth of nerve fibers

This relationship to Schwann nuclei also held for the fibers growing freely in epineurium, where fibroblastic nuclei of endoneurial type also closely followed the growing fiber, always following the Schwann nucleus and enveloping the fiber (fig 15 *C*) In the perineurial tube the growing fiber, likewise, was soon surrounded by a small tube of endoneurial nuclei, characteristic of the smaller fibroblast lying free in fibroblastic network (fig 15 *A* and *B*) These nuclei were then found nearer the growing tip than the first Schwann nucleus The distinct space between the oval fibroblastic nucleus and the nerve fiber also distinguished these embracing cells The maturation of an endoneurial sheath of the nerve fiber, including the development of myelin, was equally far advanced at the same level of nerve whether the nerve fibers were lying within the former perineurial tube or were free in the epineurium

GRAFTS OF PERINEURIAL TUBE

The possibility that the residual tube of perineurium, surrounded by epineurium, could be utilized to bridge a preformed gap between nerve ends by grafting was explored For this purpose, both the right and the left ulnar nerve in the upper forelimb of the cat were exposed at operation The right ulnar nerve was pulled out of its sheaths for a distance by the technic shown in figure 4 A corresponding length of left ulnar nerve was excised completely The perineurial tube on the right side was cut where it joined the intact nerve at each end The piece of tube thus excised was then sutured into the gap on the left side, and the piece of entire nerve from that side was sutured into the gap on the right side The suture was made with fine silk in some

experiments and with fine nylon in others Each junction consisted of two sutures one on each side of the nerve sheaths, holding the opening of the graft against the cut edge of the nerve No attempt was made to protect the suture line

The elastic tube of perineurium was found to be easy to handle in this way As will appear later, the greatest difficulty is in insuring that

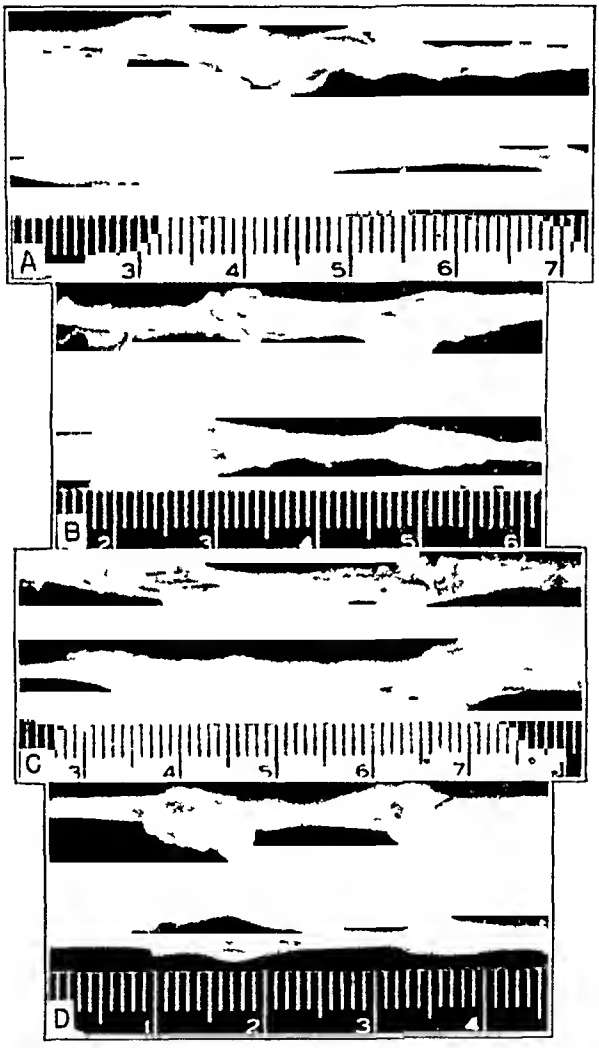


Fig 11.—Ulnar nerves (*A*) The left nerve (above) was sectioned in three places, the right nerve (below) was excised for 3 cm subperineurially ninety-nine days earlier The scale is in millimeters

B, the left nerve (above) was excised for 2.2 cm and replaced with whole graft (frozen) the right nerve (below) was excised for 2.2 cm and replaced with graft of perineurial tube (frozen) thirty-three days earlier

C, the left nerve (above) was excised for 3 cm and replaced with right ulnar nerve, the right nerve (below) was excised for 3 cm and replaced with perineurial tube from the left ulnar nerve seventy-nine days earlier

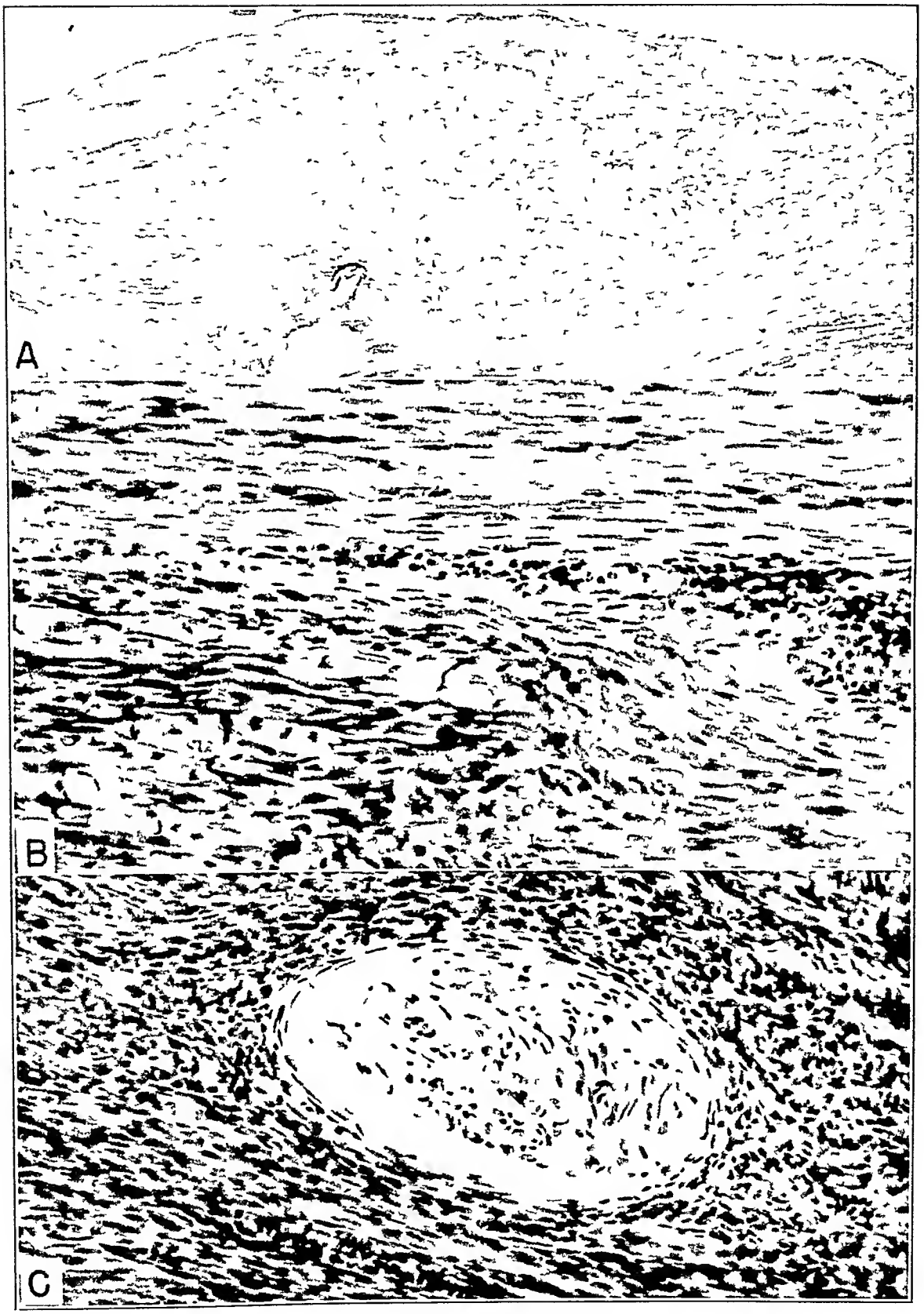
D, the left nerve (above) was excised for 2 cm and replaced with graft of whole nerve (frozen) from the other side The right nerve (below) was excised for 2 cm and replaced with graft of epineurium alone (frozen) from the other side seventy-five days earlier

the perineurium indeed remains, and section of the piece of nerve originally pulled from the tube was found to be the only way in which the procedure could be adequately controlled. If a transverse section showed more than two lamellas of perineurium adherent to the pulled fragment, it is likely that little remained in the graft.

In such an experiment a gap of 2.2 cm. of ulnar nerve was grafted on each side, and the nerves were explored on the thirty-third day, when the animal was killed. In this instance both the perineurial tube and the piece of intact nerve were frozen hard with solid carbon dioxide for five minutes and then thawed to room temperature before being sutured into position, a procedure designed to test the resistance of the grafts to preservation in vitro. At the final exploration stimulation of the ulnar nerve proximal to the graft was without effect on either side. A swelling had formed at each suture line on each side (fig. 11 *B*), and the swellings were adherent to surrounding tissue. The whole graft was swollen and adherent, whereas the perineurial graft was chiefly smooth and free from adhesions. The perineurial tube had filled out, and sections showed it filled with fine nerve fibers, oval perineurial cells (fig. 12 *A* and *B*) and small numbers of Schwann cells except at the distal extremity, where the nerve fibrils were finer and the Schwann cells few. The condition was entirely comparable to that of simple subperineurial excision of the ulnar nerve at ninety-nine days described earlier, except that maturation of the myelin sheaths had not occurred and few axons had reached the peripheral nerve.

Large numbers of nerve fibers had likewise entered the autogenous frozen graft of whole nerve on the other side. Few fibers coursed down the center of the graft, where the intercolumnar spaces were unduly wide and more tightly filled with macrophages than in simple degenerating nerve. Except at either end, the Schwann nuclei and Schwann bands of this graft stained more darkly with hematoxylin and eosin than did the normal nerve, whether they had received a regenerating fiber or not. The few Schwann nuclei accompanying nerve fibers entering and leaving the graft for 3 mm. at each end were wider and shorter than the large numbers in the remainder of the graft. The Schwann nuclei directly associated with the axis-cylinder in the middle of the graft appeared not to differ in any way from those remaining unutilized in this region. No necrosis was seen, but the perivascular spaces were greatly widened and the vessels dilated. The number of fibers successfully transmitted to the peripheral trunk by the whole graft and the number transmitted by the perineurial tube graft were approximately equal.

It was found that a small fragment of the original nerve 3.75 mm. in length had been left in the lumen of the perineurial tube and had become encysted by the pale oval endoneurial cells (fig. 12 *B*). Though



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phagocytes had engulfed the myelin in these fragments, the Schwann cells stained darkly precisely as did those of the whole nerve graft in the other limb Further, there was no evidence of division of these encysted Schwann cells or of their contribution to the cell columns (fig 12 *B*) The cells lining the cyst were the flat perineurial cells with a large pale nucleus This observation, and another from a different experiment (figs 12 *C* and 15 *D*), appear to offer further strong evidence against participation of Schwann tissue in regeneration as a primary event

The graft of whole nerve stained uniformly more densely for collagen than did normal nerve, whereas the perineurial graft showed longitudinal streaks of collagen beginning at the suture line and running throughout its length Mallory's phosphotungstic acid hematoxylin stain showed the Schwann nuclei as dark blue throughout the two grafts Those in the perineurial graft were sparsely distributed among the fibroblastic nuclei of the cells columns (fig 15 *D*), becoming rarer as the distal end of the graft was reached They clearly lay in the bundles of nerve fibers and distant from collagen (fig 15 *D*) The Schwann nuclei of the graft of whole nerve were evenly and intensely stained throughout except for 3 mm at either end, where they had been replaced by a few thicker Schwann nuclei of the type found in the scars and directly related to regenerating nerve fibers These appeared to be migrating nuclei

The surface of the perineurial graft was identical with normal epineurium and contained numbers of arterioles and venules which had connections with longitudinal vessels but not with surrounding tissue From the inner aspect of the epineurium fine fibrous overlapping bands, covered with pale oval nuclei, stretched medially and distally to the regenerated nerve bundle as though expanded laterally and distally These appeared to be the lamellas of a new perineurium, as observed in the experiments on simple avulsion

In a second experiment, 3 cm of ulnar nerve was grafted on each side, with the same technic and the animal allowed to survive seventy-nine days The grafts were permitted to cool to room temperature in saline solution before being sutured but were not otherwise treated

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EXPLANATION OF FIGURE 12

Fig 12.—*A*, section of proximal stump of the ulnar nerve grafted to perineurial tube (frozen) thirty-three days earlier, cresyl violet stain

B, section showing the distal end of a fragment of nerve found among the fibroblastic cells almost halfway between the two stumps in the experiment from which *A* was taken Hematoxylin-eosin stain

C, a similar fragment lying transversely in another experiment taken seventy-nine days after excision of the main nerve mass

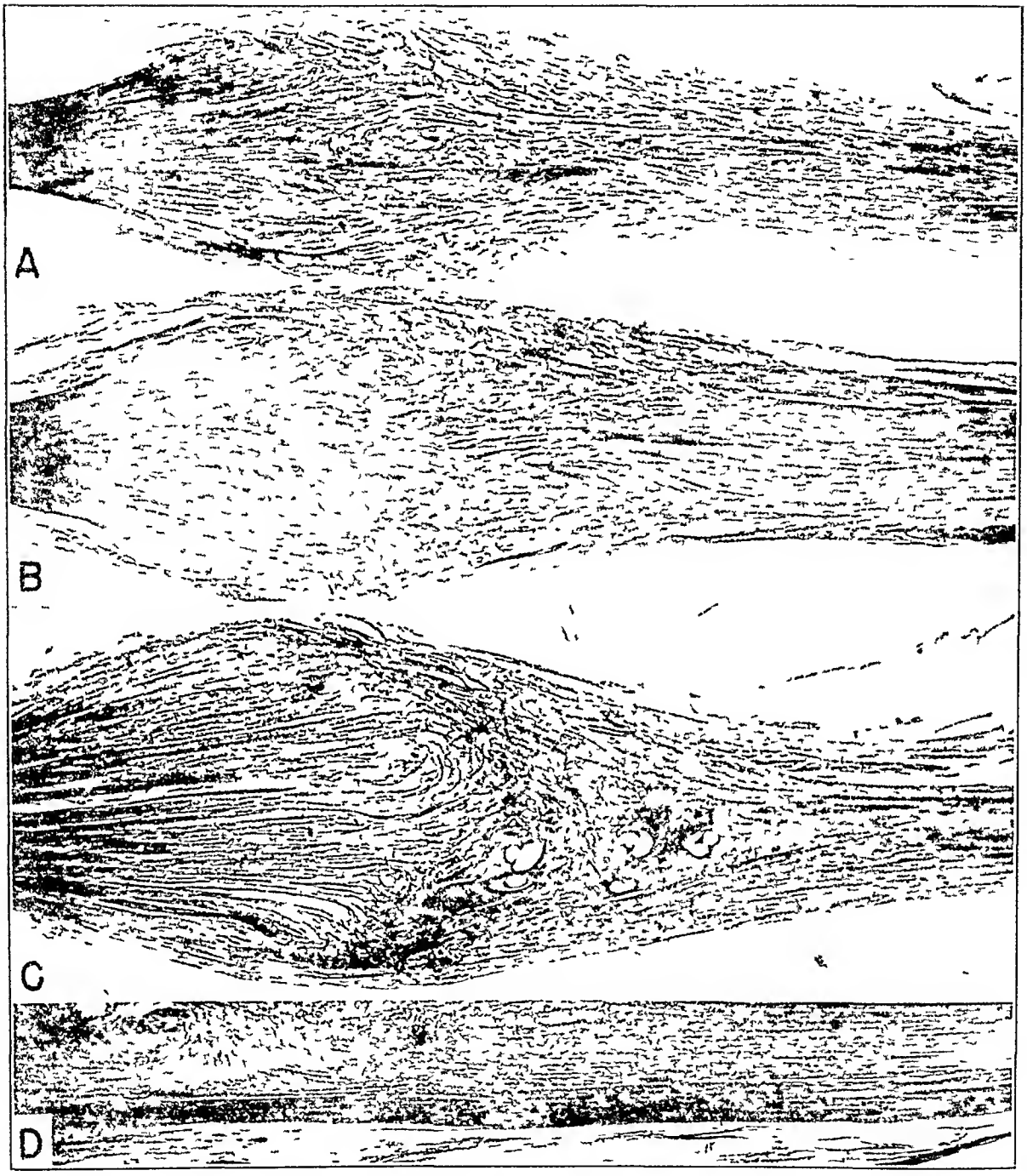


Fig 13.—*A*, proximal stump of the ulnar nerve seventy-nine days after graft of the perineurial tube from the opposite ulnar nerve Gros-Bielschowsky method, counterstained with cresyl violet

B, section near that shown in *A*, stained with phosphotungstic acid hematoxylin to show bands of collagen

C, proximal stump of the ulnar nerve seventy-five days after graft of epineurium from the opposite ulnar nerve Gros-Bielschowsky method, counterstained with hematoxylin and eosin

D, proximal stump of the ulnar nerve seventy-nine days after suture to the whole nerve graft The portion of the swelling containing a suture is not shown Gros-Bielschowsky method, cresyl violet counterstain

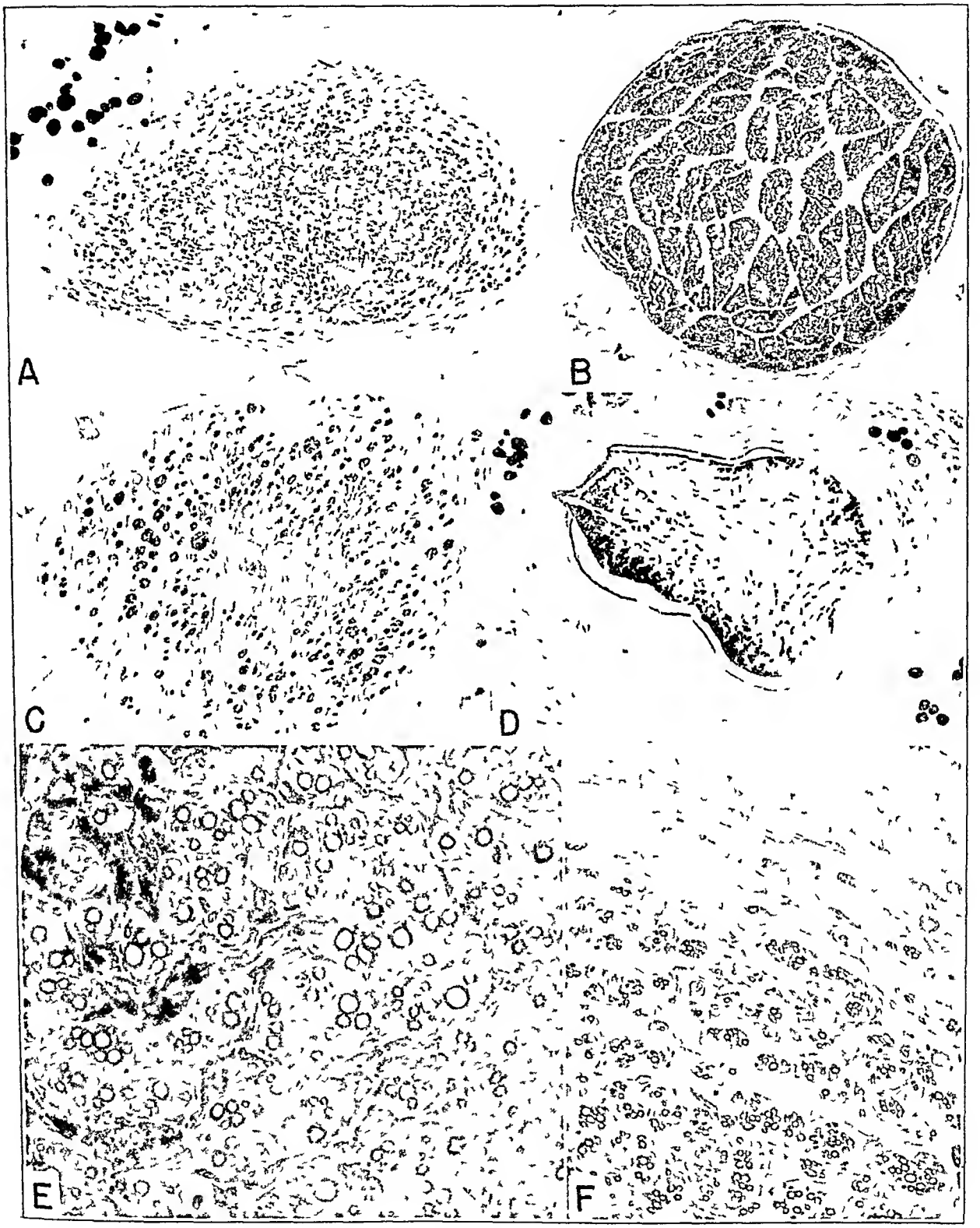
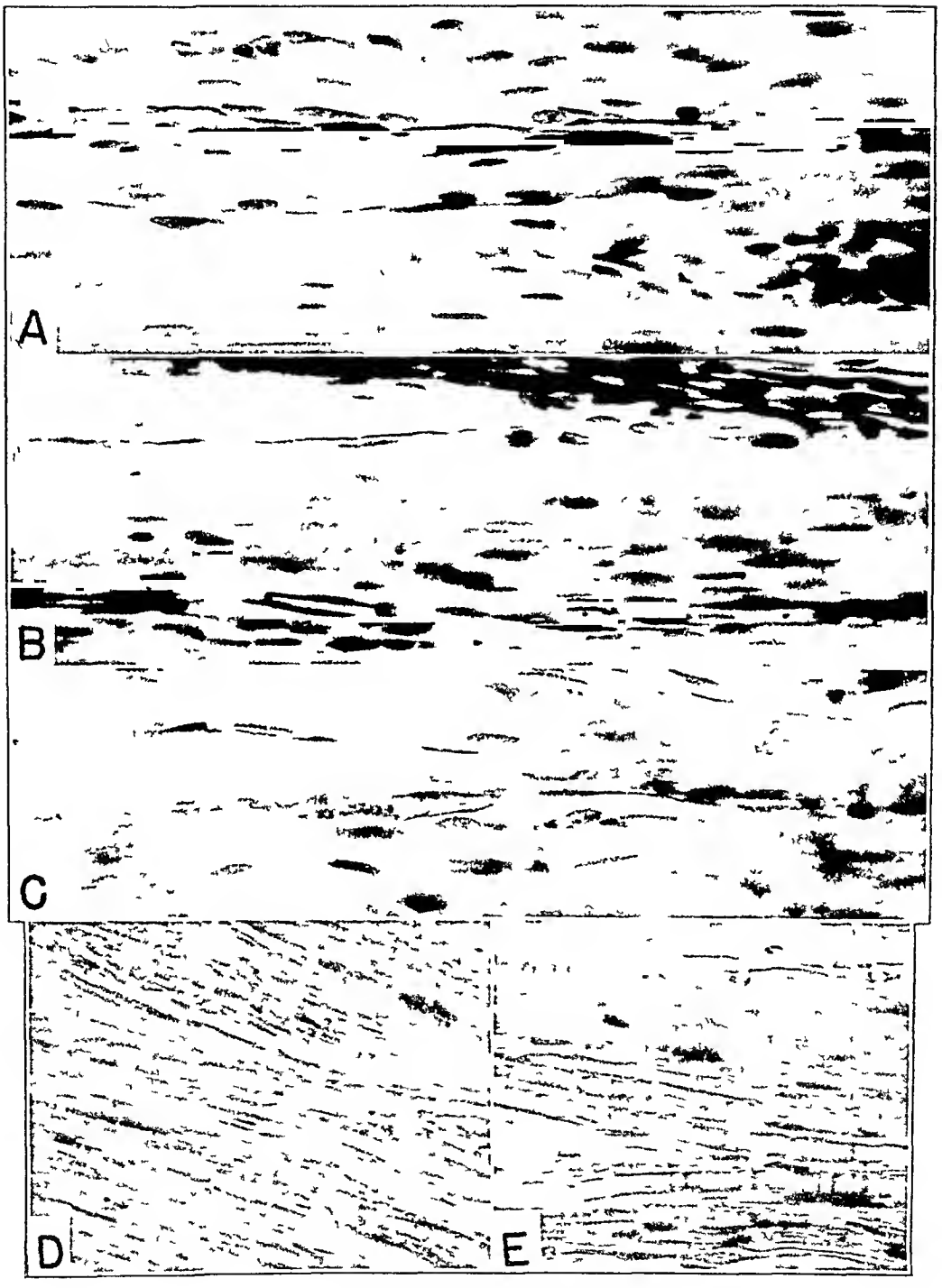


Fig 14.—Cross sections of ulnar nerve, osmic acid stain *A* middle of perineurial graft after seventy-nine days, *B*, normal nerve at the same level, *C*, middle of epineurial graft (frozen) after seventy-five days, *D*, middle of graft of whole nerve after seventy-nine days, *E*, high magnification of the center of *A*, but counterstained with eosin, *F*, higher magnification of the edge of *A*



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On the seventy-ninth day the ulnar nerves were cut proximal to the grafts and stimulated On the side of the perineurial tube graft a moderate flexion (50 per cent) of the wrist and a strong flexion (80 per cent) of digits and protrusion of the ulnar claw were produced On the side of the whole nerve graft feeble flexion (10 per cent) of the wrist and slight movement of the claw without flexion of digits occurred Both nerves showed swellings at the suture lines (fig 11 *C*), but while the right nerve (perineurial tube) had only a few filmy adhesions to muscle, the left (whole) nerve was densely adherent to all surrounding tissues and was very vascular The perineurial tube had filled out to the diameter of the parent nerve On transverse section it presented a diffuse field of medullated nerve fibers with sparse longitudinal endoneurium and beginning perineurium (fig 14 *A*, *E* and *F*) Longitudinal section showed full regeneration throughout the nerve, with good connection with the peripheral nerve (fig 13 *A*) There was no evidence of Perroncito spirals or reversal of direction, and medullation in the peripheral nerve was well balanced Collagen was distributed in longitudinal bands (fig 13 *B*)

The autogenous graft of whole nerve had remained in good apposition to the nerve ends and was conducting fibers with approximately the same stage of medullation at every level as the fibers of the perineurial graft The nerve fibers, however, mainly lay at the edge of the graft, where they were tightly packed (figs 13 *D*, 14 *D* and 16 *D*) The Schwann nuclei showed the same peculiarity of dark staining noted in other grafts of whole nerve In this graft central necrosis had occurred at two levels In each case the Schwann nuclei had disappeared, and

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EXPLANATION OF FIGURE 15

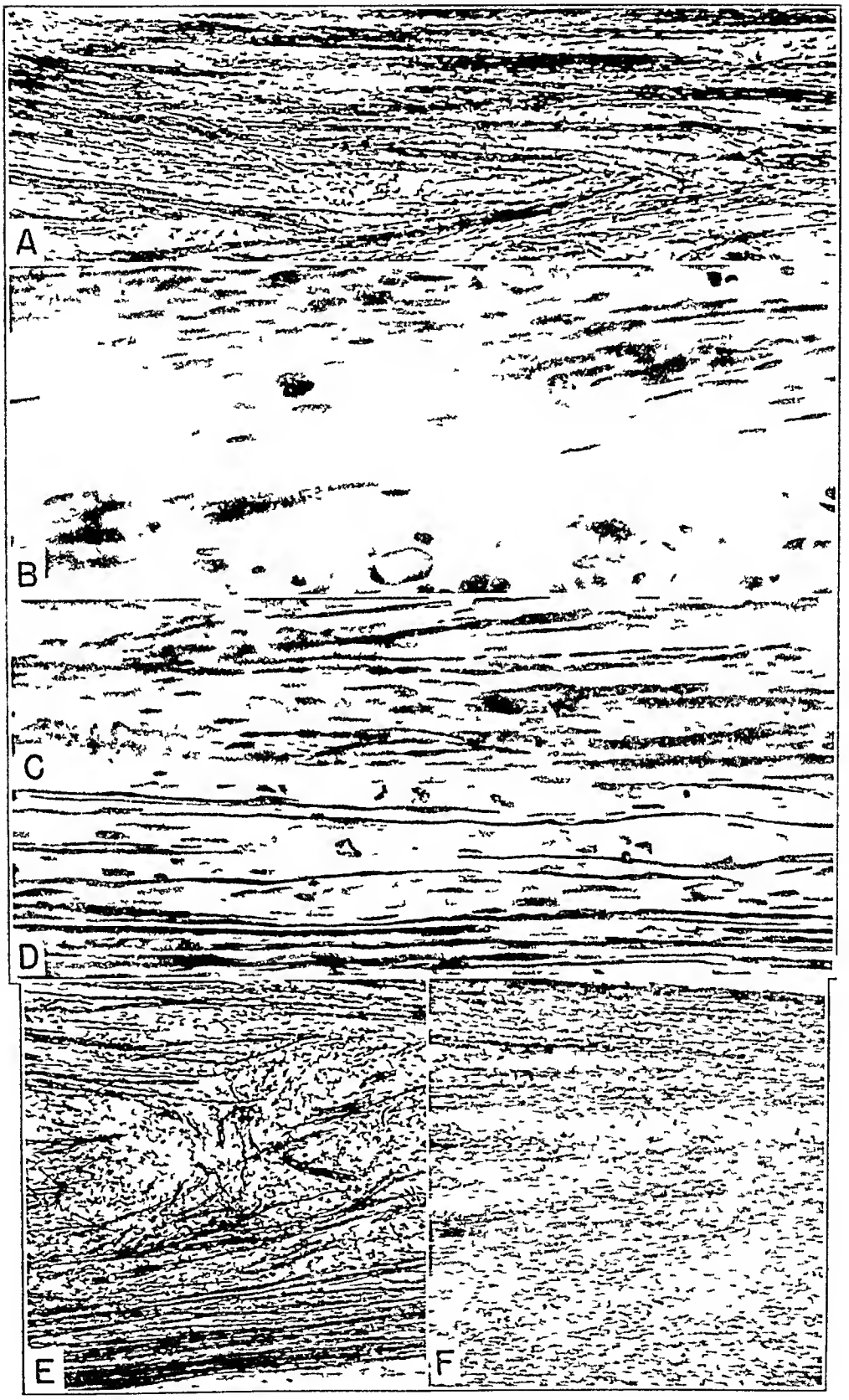
FIG 15.—*A*, distal end of ulnar nerve of a seventy-nine day perineurial graft A bundle of nerve fibers with condensation of the endoneurial sheath and fibroblastic nuclei is shown above A regenerating single fiber runs across the middle of the figure At the center is a Schwann nucleus closely applied to the axis-cylinder, the last nucleus before its growing tip, which was 0 25 mm away to the right of the figure The long oval nuclei below accompany a strand of collagen Gros-Bielschowsky method, hematoxylin-eosin counterstain

B, section similar to that in *A*, showing another terminal Schwann nucleus

C, regenerating filaments of popliteal nerve in the epineurium of the remaining peroneal nerve, eighty-eight days after excision, showing a terminal Schwann nucleus on a fiber growing between epineurial fibroblasts Note the absence of endoneurial fibroblasts around the fibril at this stage, though they accompany the bundle of fibrils below

D, section of the ulnar nerve, showing contents of perineurial tube stained with phosphotungstic acid hematoxylin (Peers's modification) An encysted fragment of the avulsed nerve lies above Of the cellular contents of the remainder of the tube (compare figure 12 *B*) only strands of collagen and a few rod-shaped Schwann nuclei in the interspaces and in the encysted fragment are stained here

E, channel between strands of collagen in regenerating peroneal nerve one hundred and six days after subperineurial avulsion, showing Schwann nuclei at the edge of developing myelin sheaths Same stain as that employed in *D*



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in 1 instance there was some cavitation, in which nerve fibers coursed irregularly and lost direction (fig 16 *E*) Dense collagen had been deposited in these areas (fig 16 *F*), and slighter collagenization was present throughout

One further experiment deserves mention on account of an instructive mishap Two centimeters of ulnar nerve was grafted on each side, as in the preceding experiments Both the perineurial graft and the whole nerve graft were frozen in solid carbon dioxide for five minutes and thawed to room temperature before suture Unfortunately, it was later found that the perineurium had been pulled with the nerve contents, leaving only epineurium The experiment, however, serves as a control of those already reported The animal was killed at the end of seventy-five days, at which time it was found that both nerves conducted motor power well, that of the short epineurial graft almost perfectly (95 per cent) and that of the whole graft moderately well (50 per cent) The epineurial graft was slender, smooth and not adherent to any structure (fig 11 *D*) The whole nerve graft was bound down to all tissues with dense and very vascular adhesions Transverse section of the epineurial graft (fig 14 C) showed that the regenerated medullated fibers lay in small discrete bundles in heavy fibrous tissue The most striking feature of the epineurial graft was the lack of mass invasion of fibroblastic tissue at the proximal suture line (fig 13 *C*) The experiment indicates the possibility of conduction of growing nerve fibers by simple fibrous tissue, provided the distance is short and the direction of fibers purely longitudinal, as in epineurium Close inspection revealed that fibers were frequently lost by reversal of direction, but as the distance was very short in this experiment it mattered little Endoneurial tissue invaded the fibrous mesh with the Schwann cells, which followed the

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EXPLANATION OF FIGURE 16

Fig 16—*A*, longitudinal section of the nerve developed within the grafted perineurial tube seen in transverse section in figure 14 *A* Gros-Bielschowsky method, counterstained with cresyl violet

B, border of the same nerve as that shown in *A*, under higher magnification, showing oblique sheets of collagen with large flat cells passing from the epineurium, below (vessels in section), to the border of the nerve, above

C higher magnification of the axis-cylinders shown in *A*, revealing beaded appearance typical of recently regenerated fibers

D, section near the edge of an autogenous graft of the ulnar nerve seventy-nine days after operation, showing the irregular caliber of the axons and their close adherence to the rodlike Schwann cells of the graft Numerous phagocytes remain Gros-Bielschowsky method, cresyl violet stain

E, section lower in the same graft as that from which *D* was taken, showing distortion and reversal of nerve fibers as they reach an area of central necrosis

F, section from the same graft, showing dense collagenization of the central necrotic area, with diffuse light deposit in the rest Hematoxylin stain The stained nuclei include those of the Schwann cells (dark rods) and those of phagocytes and, very lightly stained, those of endoneurial fibroblasts

nerve fibers to build in miniature the architecture for each small nerve bundle The graft of whole nerve on the opposite side of this animal showed the characteristics described for earlier experiments, including central necrosis

COMMENT

The differences between the cellular structure of the perineurium and that of the endoneurium are quantitative rather than qualitative Each contains, besides wandering histiocytes, two types of mesoblastic cells One of theses is a fibroblast, which is profoundly stimulated by nerve injury That proliferation of the endoneurium provided a framework for the regeneration of nerve across gaps in its continuity was advocated by Hjelt [34] in his early experiments on frog nerves, in 1860 Hassin [2] has more recently returned to this view and asserted that after degeneration of the nerve fibers most, if not all, Schwann cells of the peripheral nerve are converted to phagocytes and lost Although we do not subscribe to this view regarding the fate of the Schwann cells, the cells in the immediate vicinity of the cut ends are certainly lost The experiments cited in this paper offer evidence that the junctional tissue is provided by the fibroblasts of the endoneurium and the perineurium The view that such tissue results from proliferation of Schwann cells is disproved by the consistent staining of the nuclei of these cells with the phosphotungstic acid hematoxylin method and the proof of the relationship of these cells to axis-cylinders in alternate sections of material embedded in pyroxylin and stained with this method and with the Gros-Bielschowsky technic By the facility thus gained, the migration of such nuclei was traced after the invasion of nerve fibers Such a migration is fully consistent with the observations of Speidel [35] on amphibians The perineural lamellas are lined with large flat cells with a pale oval, or nearly circular, nucleus, larger than the fibroblast These cells are also found in the endoneurium ("fixed connective tissue cells," Domikow [31]) near blood vessels They are carried into a neural scar by the fibroblastic proliferation but retain their staining characteristics In inflammatory conditions we have seen them give rise to the macrophage In appearance and behavior they closely resemble the mesothelium of peritoneum or pleura More investigation is necessary before the character of these cells can be finally settled Perineurium and endoneurium therefore normally differ only in the

34 Hjelt, O Ueber die Regeneration der Nerven, Virchows Arch f path Anat **19** 352-367, 1860

35 Speidel, C C Studies of Living Nerves I The Movements of Individual Sheath Cells and Nerve Sprouts Correlated with the Process of Myelin Sheath Formation in Amphibian Larvae, J Exper Zool **61** 279-331, 1932, IV Growth, Regeneration, and Myelination of Peripheral Nerves in Salamanders, Biol Bull **68** 140-161, 1935

proportion of content of these two cell types The endoneurial and perineurial fibroblast appear to be identical, and we suggest that they together be called "neural fibroblasts" The neural fibroblast differs from the epineurial fibroblast in its staining properties and the type of collagen deposited

The regenerating nerve fiber is certainly free from any sheath for the first 0 25 mm unless Schwann cells are already provided, as in the distal nerve trunk It is therefore not necessary for Schwann cells to be provided for the regeneration of the nerve fiber The natural cement substance of divided nerves, the neural fibroblastic tissue, tends to lateral diffusion and the production of shapeless masses when left to sprout uncontrolled The mesothelium which normally limits it is drawn into a mixture from which it cannot reform a membrane, except around individual nerve fibers

In epineurium the nerve fiber was found to be regularly accompanied with two distinct types of cells to within 0 25 mm of its growing tip One of these was the elongated nucleus of Schwann, closely applied to the fibril, which was thickened at or just beyond the Schwann nucleus The other, which always lay separated from the fibril by a space was a cell with oval, pale nucleus, often curved so as partly to embrace the fibril in its concavity This inner sheath cell appeared to be the neural fibroblast, though the large perineurial cells commonly formed a further covering

A tube of perineurium, formed by extraction of the contained nerve bundle, condenses to form a column of fibroblastic cells, the core of which differs considerably in appearance from that of simple fibrous tissue or epineurium but is identical with the neural fibroblast, whose proliferation from the nerve stumps contributes further cells at each end The specialized cells of this core conduct regenerating nerve fibers without obstruction, and those nearest appear to become immediately oriented to the regenerated fibril so as to enclose it in a tube From the fibroblastic network the entry of nerve fibers thus produces a multitude of small fibroblastic tubes Many nerve fibers of later arrival enter tubes already in formation, so that in time each tube contains a group of nerve fibers, one or two of which are more mature than the others The large flat perineurial cell evidently has a remarkable propensity for encysting Schwann tissue, for instances of envelopment of dead residual fragments of the avulsed nerve bundle were seen This points to some specific attraction which collects these cells from the mixed matrix

This process of regeneration of nerve fibers within a preformed perineurial tube differs from growth free in scar in that lateral escape of the nerve fibers is prevented and the loose central network provides a path of least resistance as compared with the fibrous epineurial cov-

ering Small bundles do undoubtedly escape from the main group, but in the greater resistance of the epineurium they have a greater opportunity of reentry to the core than of defeat or reversal The main bundle thus formed tends to split into from two to six subsidiary bundles after the first centimeter, but each of these bundles remains large and compact as compared with the many fine bundles which form in epineurial fibrous tissue

The regenerated nerve within a perineurial tube appears to determine its own diameter according to the number of fibers conducted Transverse or circular fibrosis was not found, and the longitudinal lacework of the epineurium is not such as to prevent lateral expansion of the contents On the other hand, the new nerve fibers lack the absolutely parallel course they pursue in a nerve graft or a peripheral degenerated nerve The zigzag course pursued by each fiber did not affect its rate of growth or of maturation

The experiments demonstrate, therefore, that regeneration of nerve can occur rapidly and efficiently in a framework provided by the perineurium and that the Schwann sheath can be efficiently and automatically provided for a whole bundle of nerve fibers where none previously existed The mode of production of Schwann cells in these circumstances is uncertain, but the lack of accumulation of cells at any one point suggests that they are provided by repeated budding of the most distal nuclei

The interior of the newly formed nerve bundle contains more collagen than does normal nerve, and the presence of broad strands of this substance tends to break up the new nerve into separate bundles after the first 1 to 3 cm The strands of collagen lie longitudinally and it would appear that the longer the fibroblastic tissue remains inactive the more such strands are formed Tension, probably through the more prolonged ischemia thus produced, increases the amount of collagen in perineurial grafts, as in grafts of whole nerve In the absence of inflammatory reaction, like that which surrounds a ligature which pierces the tube, diffuse collagen formation, such as occurs in grafts, does not occur within the perineurial tube In the autografts of whole nerve in these experiments there was considerable shrinkage, with the appearance of diffuse collagen This change was associated with reactive changes in the endoneurial fibroblasts, such as Brenner and I have also noted in ischemia due to pressure [26] and percussion [18] but of greater severity Such change is held responsible for the uneven caliber of axis-cylinders in grafts of whole nerve The perineurial tube grafts had not undergone this transformation, possibly because no old framework existed for subsequent condensation A similar change at a longer interval in such grafts is considered unlikely, for robust nerve fibers had already established their own loose collagenous "tubes"

In recording their disappointing experience with homografts, Seddon and Holmes[9] suggested the possibility of a specific tissue immunity as the cause of the complete collagenization in and around the graft, for such an extreme change did not occur in animal experiments. In experiments which my colleagues and I have conducted diffuse collagenization had occurred even in autografts, and we are disposed to regard the process as a result of inflammatory reaction, differing only in degree in different kinds of grafts. The distribution of nerve fibers at the periphery in partly successful grafts indicates that vascular factors enter into the process, but inflammatory reaction is also influenced by these factors, and we are impressed by the frequent narrowing of axis-cylinders in the areas where vascular supply is presumed to have been adequate.

From our experiments we are convinced that no cut nerve end remains of normal structure. Schwann cells are lost for at least 3 mm. and damaged for 1 or 2 cm. Fibroblastic proliferation is inevitable in this region, and usually for a much greater distance. Connective tissue does not invade nerve sutures or grafts, it is there already. The factors which make for collagenization are those that influence the maturation of the endoneurial and perineurial fibroblast. The first of these is the age of the cell, and this must be considered in relation to the opportunity of the cell to undergo specialized development. There is good evidence that the young fibroblast when allowed to redevelop its specialized function as sheath to a nerve fiber will do so to perfection. The older cells lying in clumps appear to become surrounded by collagen, and this thickens into coarse strands as the nuclei assume their resting staining characteristics. The distal fibroblastic mass in a perineurial graft is already more dense after three months, and this process, which manifestly depends on the time elapsed before nerve fibers reach the peripheral end, limits the useful length of the perineurial tube. This possibility did not occur in our experiments, but it could be overcome if necessary by excision and renewal of the peripheral junction. The remaining factors known to affect the development of fibroblasts are tension and ischemia and are probably interrelated. Both should be avoided as completely as possible in all sutures and grafts.

The possible practical utility of perineurial tubes for bridging gaps in human nerves raises two immediate questions, namely the estimation of the ultimate efficiency of such grafts, and the problem of securing adequate perineurial tube for human nerve.

The question of efficiency of nerve graft can finally be settled only in human experiments, for it has been abundantly demonstrated that the nerves in animals show astonishing power of regeneration through all manner of gaps and obstacles. The crossing of a gap of 3 cm. in a small animal may mean regeneration through half the extent of a limb,

but the factors involved appear to correspond to those active in the same absolute length of gap in man With this qualification in view, however, one may indicate the salient points of a comparison between a perineurial tube graft and an autogenous whole nerve graft

My own experiments showed that fresh autogenous nerve graft underwent a tissue reaction which caused shrinkage and collagenization These grafts, nevertheless, conducted nerve fibers on which myelin matured in a natural manner, but the grouping of fibers at the periphery and the shrinkage indicated that the graft would not transmit the number of fibers it originally contained and the fibers were irregular in caliber The adherence of epineurium to surrounding structures deprived the nerve of freedom of movement

The perineurial graft, on the other hand, was not adherent to surrounding tissue except at the suture lines, and these could undoubtedly be perfected by utilization of one or another of the existing intubation technics [36] The slender structure of the graft enables revascularization to be rapid, and its probable metabolic rate suggests the possibility of survival for a long period by diffusion alone There appears no reason to make its diameter approximate that of the recipient nerve except so far as its opening may stretch over the nerve end It is moderately extensible and has no physiologic limit to length It certainly undergoes fibrous partition after the first 10 mm, but the partition is vertical and does not give evidence of limiting the development of nerve fibers The resulting nerve bundles are not strictly parallel, but this feature did not in my experiments emerge as of any importance in ultimate conductile efficiency

The most obvious disadvantages appear in the experiments here recorded It is difficult to be sure that sufficient lamellated perineurial sheath remains to form a lining to the tube This can be satisfactorily determined only by transverse section of the nerve substance withdrawn from the tube The greatest difficulty is in finding a donor nerve with sufficient length within one perineurial compartment Few nerves travel far within a single perineurial sheath before undergoing fascicular division A single large trunk in man, such as the posterior tibial nerve is found on section to consist of seven to ten small fasciculi, each with a separate perineurium The ulnar nerve, usually a single fasciculus in the cat and monkey from the brachial plexus to just above the elbow, sometimes divides into two or three fasciculi at the midhumeral level in man More success is likely with selection of one of the largest of the fasciculi of the sciatic nerve, which run distances of many centimeters before regrouping and are clearly visible to the naked eye The perineurium and epineurium are extremely resistant to cold as com-

36 Weiss, footnotes 4 and 17

pared with Schwann cells, and it should be possible to use the frozen-dried or a similar technic[37] with success in amputation or autopsy material For autografts only short lengths of sural nerve appear possible, for this nerve usually runs in two perineurial sheaths for 6 inches (15 cm) or more A complete survey of the structure of the perineurial sheath of all cutaneous nerves in man would appear to be desirable if this procedure is considered of practical importance

The relatively short survival periods employed in the present experiments is due to my assignment to duties overseas My colleagues and I have carried out a homograft and subperineurial excisions of extreme length (9 5 cm) in macaque monkeys, but it will be many months before adequate assessment can occur, and the results will be reported at a later time

CONCLUSIONS

1 The perineurium and endoneurium of peripheral nerve are formed of specialized connective tissue cells of two types One is a large flat cell of mesothelial type, seen typically in the perineurial lamellas The other is a specialized fibroblast

2 The Schwann cells play only a subsidiary part in the regeneration of nerve The neural fibroblast is immediately activated by injury and then proliferates It invariably accompanies regenerating nerve fibers, often preceding them, and ensheaths newly formed nerve fibers and bundles The large flat mesothelial cells provide an outer perineurium

3 The uncontrolled migration of these mesoblastic cells is responsible for the traumatic neuroma Dispersal can be prevented by the provision of an intact perineurial sheath

4 The fibrosis of suture lines and grafts is associated with previous activity of the neural fibroblast Factors of importance in the production of collagen by these cells when once activated are ischemia, tension and their aging without provision of nerve fibers

5 The perineurium can be utilized for efficient repair of defects in nerve

Boston City Hospital

37 Weiss, P , and Taylor, A C Repair of Peripheral Nerves by Grafts of Frozen-Dried Nerves, Proc Soc Exper Biol & Med **52**:326-328, 1943, Histomechanical Analysis of Nerve Reunion in the Rat After Tubular Splicing, Arch Surg **47** 419-447 (Nov) 1943

VASOPARALYSIS AND VASOTHROMBOSIS OF THE BRAIN IN INFANCY AND IN EARLY CHILDHOOD

I MARK SCHEINKER, M D
CINCINNATI

THE current teaching of a large number of pathologists in regard to lesions of the central nervous system might be summed up in the doctrine that in the absence of organic disease of blood vessels such as arteriosclerosis or syphilis, the alterations in nerve tissue must be interpreted as "primary degenerative" or "toxic" The main interest in the vascular lesions of the brain has always been centered on the organic type of arterial disease Only recently has attention been called to the importance of so-called functional or reversible, circulatory disturbances, described as "vasoparalysis' [1] and "vasothrombosis" [2] It has been pointed out that a change in caliber of a blood vessel might, under certain circumstances, be as detrimental to the brain tissue as a mechanical obstruction caused by arteriosclerosis Obviously, mere dilatation of an otherwise normal vessel is not evidence of vascular abnormality A certain degree of congestion may be physiologic However if dilatation and congestion occur in combination with signs of stasis and are associated with increased permeability of the vessel wall for serous fluid and red blood cells, they would appear to be significant in the production of histologic lesions Such alterations cannot be imitated by postmortem change

The present report aims to emphasize the significance of functional circulatory disturbances in the central nervous system of infancy and early childhood The following 3 cases of "encephalitis' illustrate the clinical symptoms and the pathophysiologic mechanism of functional circulatory disturbances in three different phases of development

REPORT OF CASES

CASE 1 —A 3 year old Negro girl had been well until the day prior to her admission to the hospital, when it was noted that she vomited intermittently

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine

1 Scheinker, I M Vasoparalysis of the Central Nervous System A Characteristic Vascular Syndrome, Arch Neurol & Psychiat **52** 43 (July) 1944

2 Scheinker, I M Vasothrombosis of the Central Nervous System A Characteristic Vascular Syndrome Caused by a Prolonged State of Vasoparalysis, Arch Neurol & Psychiat **53** 171 (March) 1945

throughout the day, became drowsy and had generalized convulsions The child had had a normal birth and was normally developed She was "bright" mentally The only illnesses had been mumps and measles four months before this admission In the receiving ward the patient's temperature was 99 4 F rectally On reaching the ward, the child was having convulsions, and the temperature was 100 4 F Fit succeeded fit despite seven intramuscular injections of phenobarbital sodium,

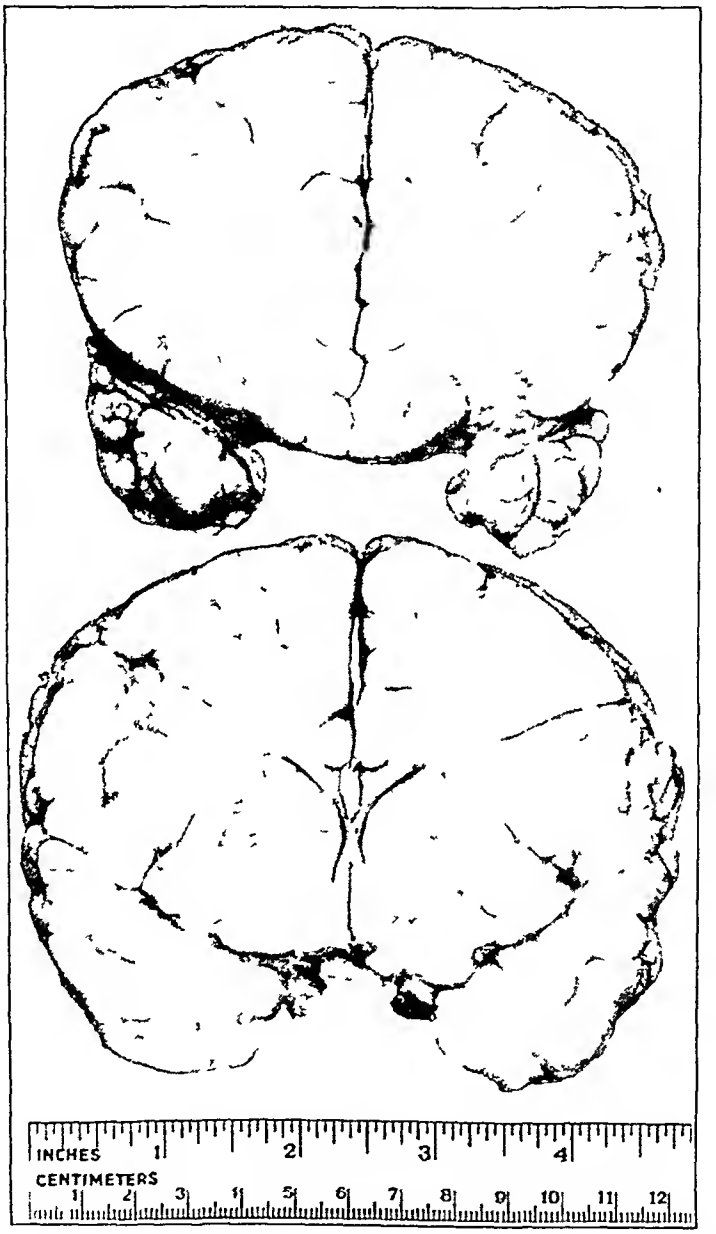

Fig 1 (case 1) —Coronal sections through both hemispheres, displaying fulness of the white matter and compression of the lateral ventricles

each of 1 gram (65 mg) She was in coma between seizures The attacks lasted from five to ten minutes, beginning in the right or the left side of the face or in the right upper extremity The deep reflexes could not be obtained The pupils were fixed to light

The temperature, which was only slightly elevated on her admission, rose to 103 F five hours later and to 105 F seven hours after admission The pulse

rate rose with the temperature and became irregular, respiration soon became fast and was labored Periods of apnea were noted twelve hours after entry

The child never roused from coma and died after thirty-seven hours in the hospital, despite symptomatic supportive therapy

Laboratory Data—A single urinalysis revealed sugar and acetone The white blood cell count was 18,000 leukocytes on two occasions, of which 50 per cent were lymphocytes, the hemoglobin measured 11 Gm per hundred cubic centimeters, the Kahn reaction of the blood was negative Determinations of the blood

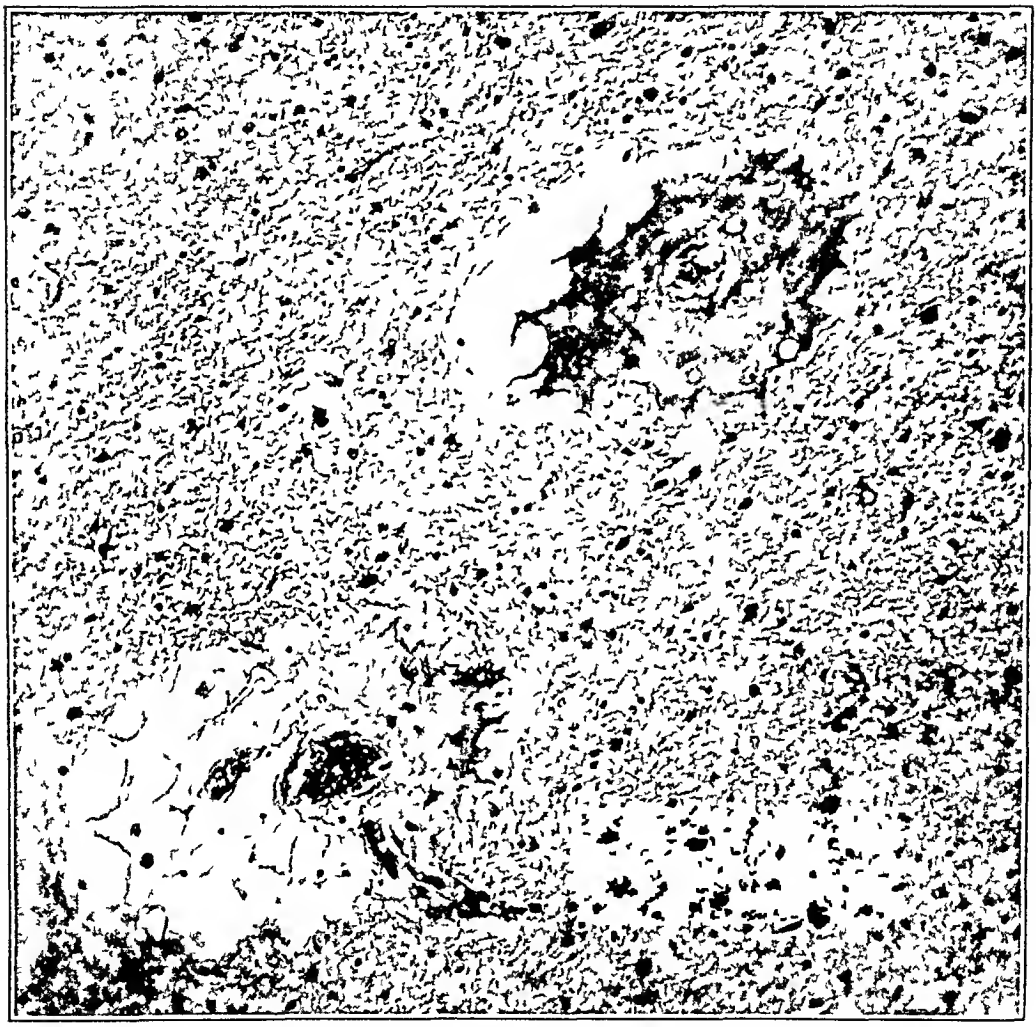

Fig 2 (case 1)—Tremendous distention of the perivascular spaces with the large masses of transudated serous fluid Note the absence of edema in the adjacent nerve tissue Hematoxylin and eosin stain, × 160

sugar, made on the successive days, were 200 and 153 mg per hundred cubic centimeters, respectively, the carbon dioxide-combining power on the final day was 34 5 volumes per cent The blood culture proved sterile

The first spinal puncture revealed a pressure of 185 mm of water, and 10 cc of bloody fluid was obtained, containing 32,000 erythrocytes and 150 white blood cells per cubic millimeter The tap was repeated ten hours later, when the child

was having labored respiration with periodic apnea Clear spinal fluid was obtained, under a pressure of 390 mm of water, the cell count was 250 erythrocytes and 29 white blood cells per cubic millimeter, the protein measured 200 mg, the sugar 132 mg and the chlorides 774 mg per hundred cubic centimeters This specimen of spinal fluid was obtained after the administration of three

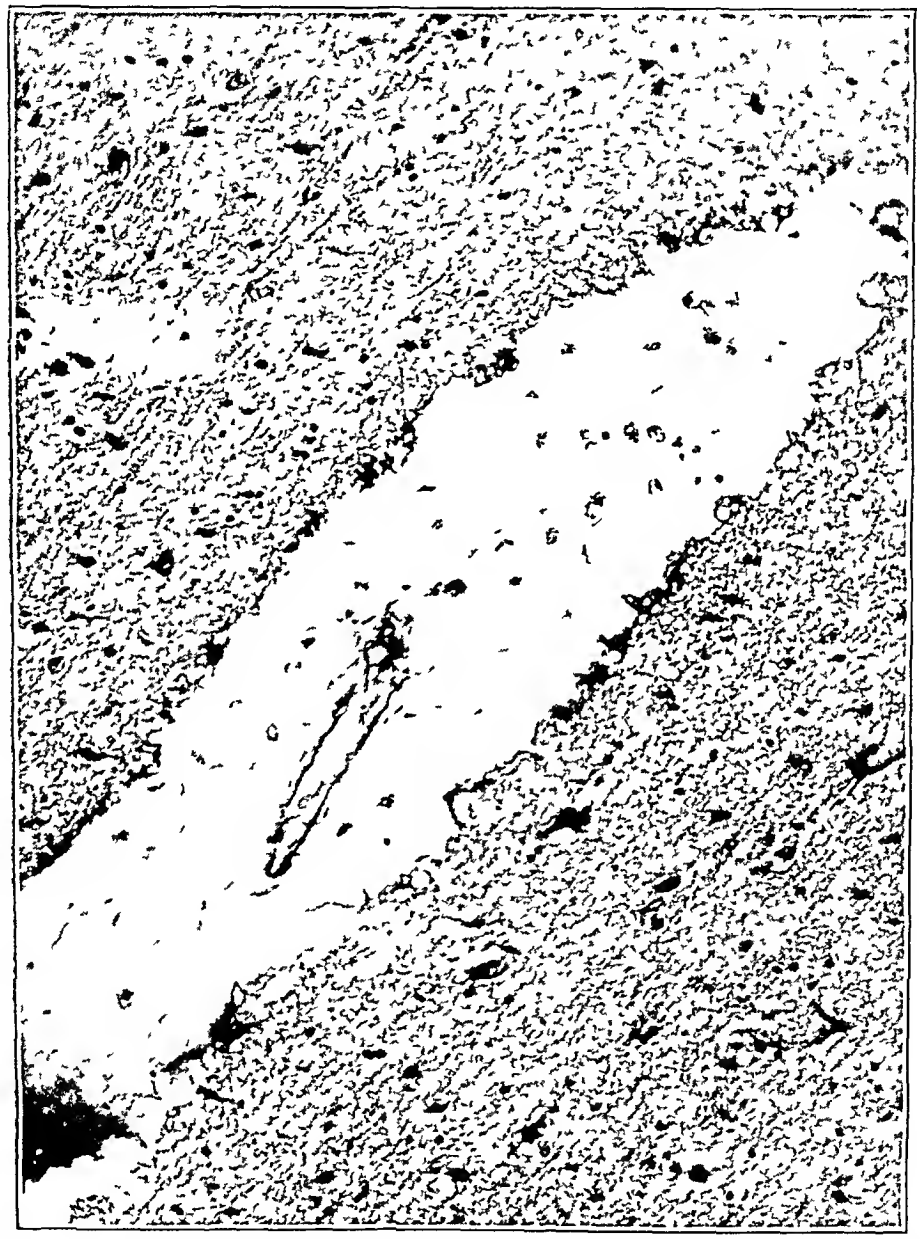

Fig 3 (case 1) —Extremely distended perivascular space, harboring gitter cells Note the early stage of liquefaction of the surrounding tissue Hematoxylin and eosin stain, × 220

infusions of a 5 per cent solution of dextrose, the last having been begun one and a quarter hours before the lumbar puncture

Autopsy—The pathologic changes, exclusive of those of the nervous system, were pulmonary edema and cloudy swelling of the cells of the liver, heart and kidneys

Gross Examination of the Brain The brain appeared generally full, the gyri were flattened and broadened, the sulci were partially obliterated There was a slight accumulation of serous fluid about some of the major cerebral veins The leptomeninges appeared otherwise normal The under surfaces of the several lobes were not remarkable except for bilateral uncal herniation of moderate degree

Coronal sections through both hemispheres displayed an obvious fulness of the white matter and compression of the ventricles (fig 1) There was a slight degree of congestion of the vessels of the centrum semiovale

Microscopic Examination Sections were taken from several areas of the gray and the white matter of both hemispheres and from the basal ganglia, medulla and cerebellum Sections from all these areas were stained with hematoxylin and eosin and cresyl violet, the Loyez stain for myelin sheaths and the Bodian 1 per cent Protargol (strong protein silver) method

Microscopic examination disclosed the same alterations throughout both hemispheres The most striking was the tremendous distention of the perivascular spaces (figs 2 and 3) They harbored large masses of serous fluid and a small number of gitter cells As a rule the transudation of serous fluid was confined to the Virchow-Robin spaces Occasionally, however, disruption of the limiting glial membrane had taken place, with escape of serous fluid into adjacent parenchyma The blood vessels revealed only a slight loss of stainability of their cellular elements There was no perivascular cuffing The vascular alterations were noted throughout the subcortical and the central white matter and were seen chiefly in medium-sized and small veins

Alteration of the nerve parenchyma, secondary to the circulatory disturbances, was perivenous in distribution and was generally seen in the immediate vicinity of the blood vessels The myelin sheaths showed degenerative alterations in the form of globular swelling, irregular outline or complete loss of stainability The nerve fibers suffered correspondingly in the same perivascular areas There was an appreciable reduction in the number of axons, the remaining fibers disclosed degenerative lesions, characterized by swelling, tortuosity and occasional splitting of some of the axons The glia showed ameboid degeneration and clasmatodendrosis

The cerebral cortex and the leptomeninges were normal

Case 2.—A 5 month old white girl was admitted to the Cincinnati General Hospital on Aug 12, 1944 She had been irritable, restless and crying for three days and nights On the evening of August 10 a physician had found the baby normal On the morning of August 12 there developed irregular, shallow and labored respirations, which led to the child's admission

On her admission she was in coma and cyanotic, the respiratory rate was about 150 per minute, the pulse rate was 150, and the temperature was 108 F The extremities were cool, whereas the trunk was hot The feet were strongly plantar flexed The examination could not be thorough, since the condition of the child was precarious She survived less than twelve hours after admission Therapy included oxygen, intravenous administration of fluids and vigorous efforts to control the hyperpyrexia, the temperature being 107 to 109 F

Laboratory Data.—The urine was normal The white blood cell count was 22,400, with a lymphocyte count of 56 per cent The hemoglobin was 9 Gm per hundred cubic centimeters The blood culture was sterile Culture of stools showed no typhoid or dysentery organisms The blood carbon dioxide–combining power of the blood was 27 volumes per cent

Lumbar puncture revealed a normal condition of the spinal fluid

Autopsy—The pathologic condition found, exclusive of changes in the nervous system, was bronchopneumonia

Gross Examination of the Brain Inspection revealed slight fulness and broadening of both hemispheres The pertinent gross changes are well illustrated in figure 4 Most of the sections of the brain disclosed numerous disseminated hemorrhages ranging from the size of a pinpoint to 2 mm in diameter They were confined to the subcortical and the central white matter The cortical gray

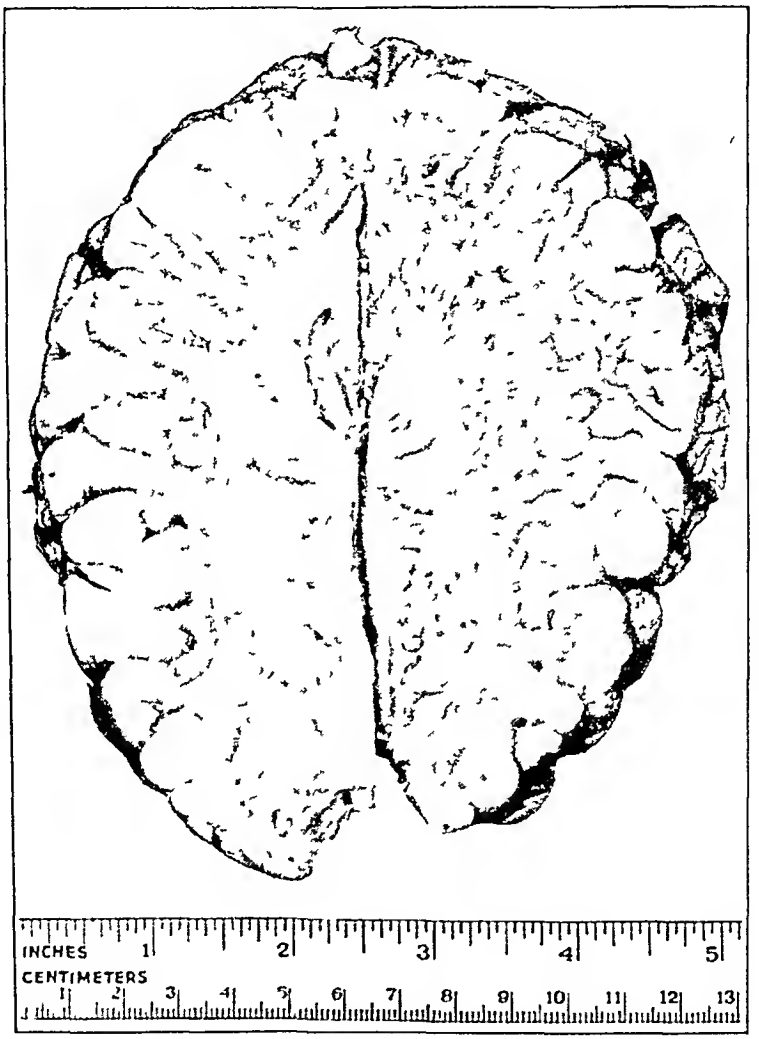

Fig 4 (case 2)—Horizontal section through both hemispheres, showing a large number of pinpoint hemorrhagic lesions, chiefly confined to the white matter

matter and the basal ganglia were relatively well preserved The cerebellum showed marked congestion and a few scattered petechial hemorrhages in the vicinity of the dentate nuclei

Microscopic Examination The microscopic changes were essentially the same in all parts of the white matter, varying only in degree What had appeared to be punctate hemorrhages were found under low power magnification to be large rings of extravasated blood about tremendously congested small veins and capillaries (fig 5) A closer examination of the blood vessels of the white matter

revealed changes typical of vasoparalysis The veins and capillaries were maximally distended and congested and disclosed signs of stasis (fig 6) The walls of the distended veins were undergoing disorganization and showed an increase of permeability for serous fluid and red blood cells The perivascular spaces appeared distended and filled with extravasated red blood cells (fig 6) In those areas in which the extravasation of blood was especially pronounced disruption of the

Fig 5 (case 2) —Numerous perivascular hemorrhages Note the distention of the perivascular spaces, which harbor large masses of extravasated red blood cells Cresyl violet stain, × 160

limiting glial membrane had occurred, this resulted in diffuse invasion of the adjacent nerve parenchyma by large masses of red blood cells and blood pigment (fig 5) The cortical gray matter was fairly well preserved except for a moderate degree of edema The leptomeninges were distended, and the pial blood vessels were congested No signs of inflammation could be detected

CASE 3.—A 4 week old white infant was admitted to the hospital on Nov 23, 1944 because of severe watery diarrhea of two days' duration, associated with drowsiness and listlessness. The infant was apparently normal at birth. The mother had had syphilis. She had received 1,000,000 Oxford units of penicillin two weeks prior to delivery. The infant was first admitted to the hospital on

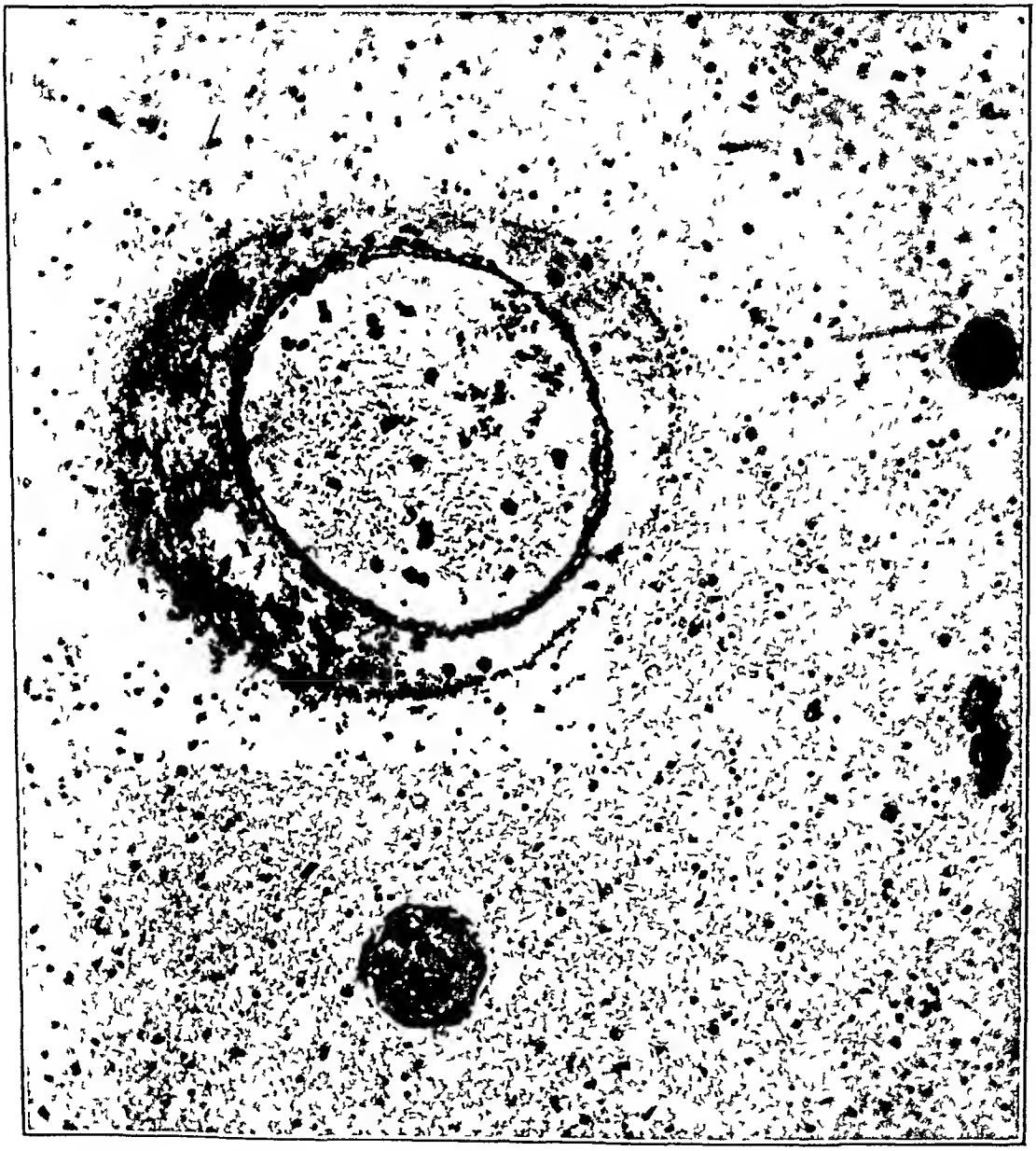

FIG. 6 (case 2).—A small vein and capillary of the white matter with typical signs of vasoparalysis. Note the evidence of congestion and stasis, associated with an early stage of degeneration of the vessel wall and increased permeability for red blood cells. The distended perivascular space is filled with extravasated blood. Cresyl violet, × 160.

Oct. 16, 1944 because of a diffuse cutaneous rash and a few small, scaly lesions around the penis and scrotum. Repeated dark field examinations of the lesions of the penis gave negative results, and the Wassermann and Kahn reactions of the blood were negative. The cutaneous lesions disappeared almost completely within

a few days, and the baby was apparently well until two days prior to his present admission

On examination the baby appeared very ill, drowsy and listless There were a severe state of dehydration, acidosis and signs of circulatory collapse He was treated with intravenous drip of dextrose in isotonic solution of sodium chloride

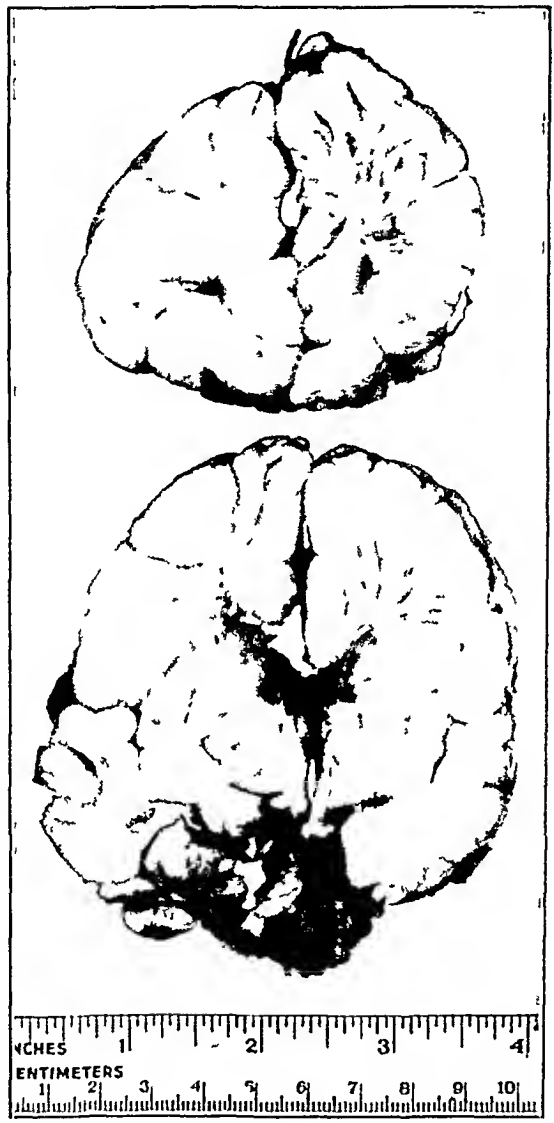

Fig 7 (case 3) —Coronal sections through the brain, with extensive areas of hemorrhagic softening involving the caudate nucleus on both sides Note the congestion of the central white matter in both frontal lobes

and was given sodium bicarbonate intravenously in order to correct the acidosis On the following day he seemed somewhat improved The carbon dioxide–combining power was 35 volumes per cent During the first three days the baby was afebrile On the fourth day in the hospital the temperature began to rise and remained elevated (102 F) until his death He became extremely listless, apathetic

and semicomatose On the fourteenth day in the hospital his breathing became rapid and irregular, and he died

Autopsy—The pathologic conditions observed, exclusive of those of the brain, were pneumonia and congestion of the liver and kidneys No signs of syphilis were found

Fig 8 (case 3)—Medium-sized vein of the white matter occluded by a thrombus Note the absence of structural changes in the wall of the vessel Hematoxylin-eosin stain, × 220

Gross Examination of the Brain The larger pial veins were found to be tremendously distended and congested The right temporal lobe appeared very full, and there was a definite shift of the midline structures to the left A well defined herniation of the uncus, measuring 2 3 cm in length and 1 5 cm in width, was present in the right temporal lobe The configuration of the circle of Willis was normal Coronal sections revealed extensive areas of hemorrhagic softening

immediately about both lateral ventricles, involving the caudate nuclei and the underlying striate bodies (fig 7) The white matter of both hemispheres displayed congestion of the smaller blood vessels and numerous petechial hemorrhages The right temporal lobe was soft to touch

Microscopic Examination of Brain Histologic examination of sections taken from several areas of the gray and white matter of both hemispheres and from

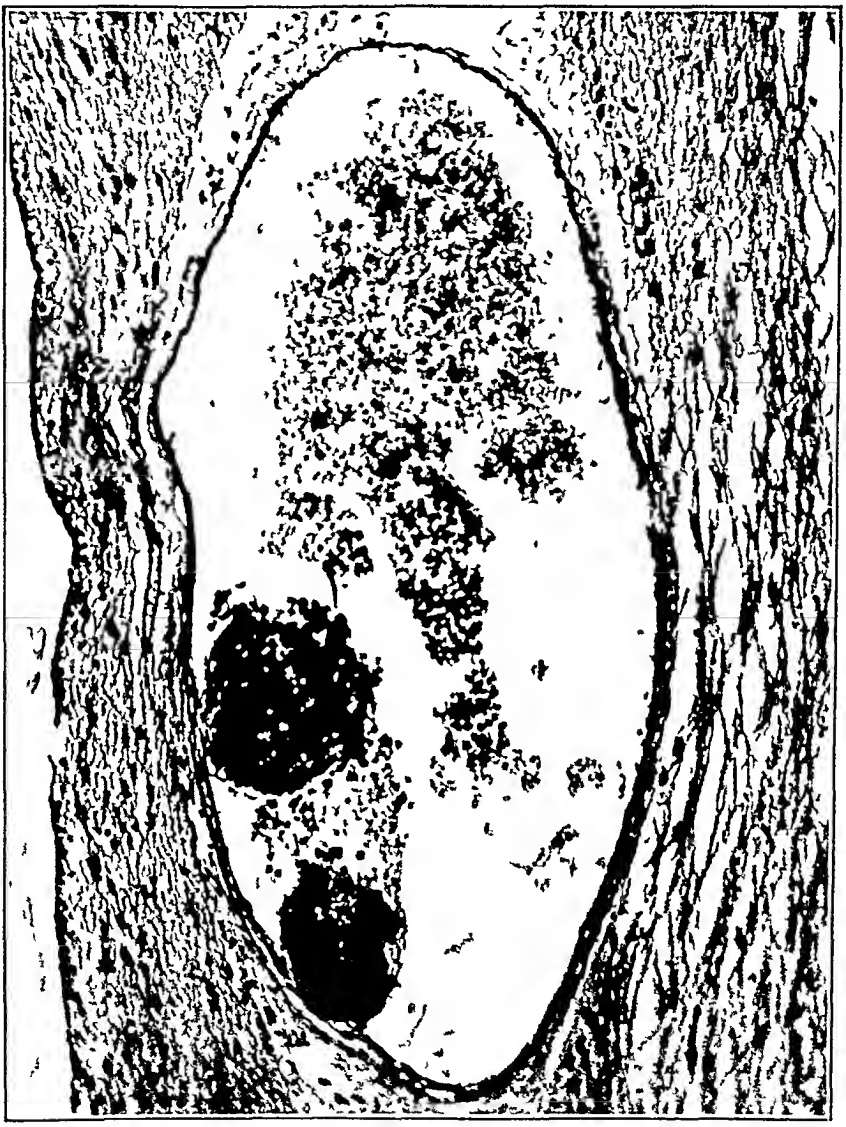

Fig 9 (case 3) —Early stage of thrombosis of a vein The blood clot is only slightly atached to the intima Note the rarefaction and necrosis of the surrounding nerve tissue Hematoxylin and eosin stain, × 220

the basal ganglia disclosed vascular lesions and alterations of the nerve tissue proper The most striking manifestation of the circulatory disturbances was the presence of various stages of venous occlusion, as illustrated in figures 8, 9, 10 and 11 The lumens of numerous small veins were occluded with blood clots,

composed of curved strands of fibrin mixed with large masses of white and red blood cells The clot seemed to be only slightly attached to the intima The walls of the vessels themselves appeared well preserved No signs of inflammation could be detected In some of the veins it seemed possible to trace the thrombus formation from its beginning Figure 9 shows a medium-sized vein, tremendously

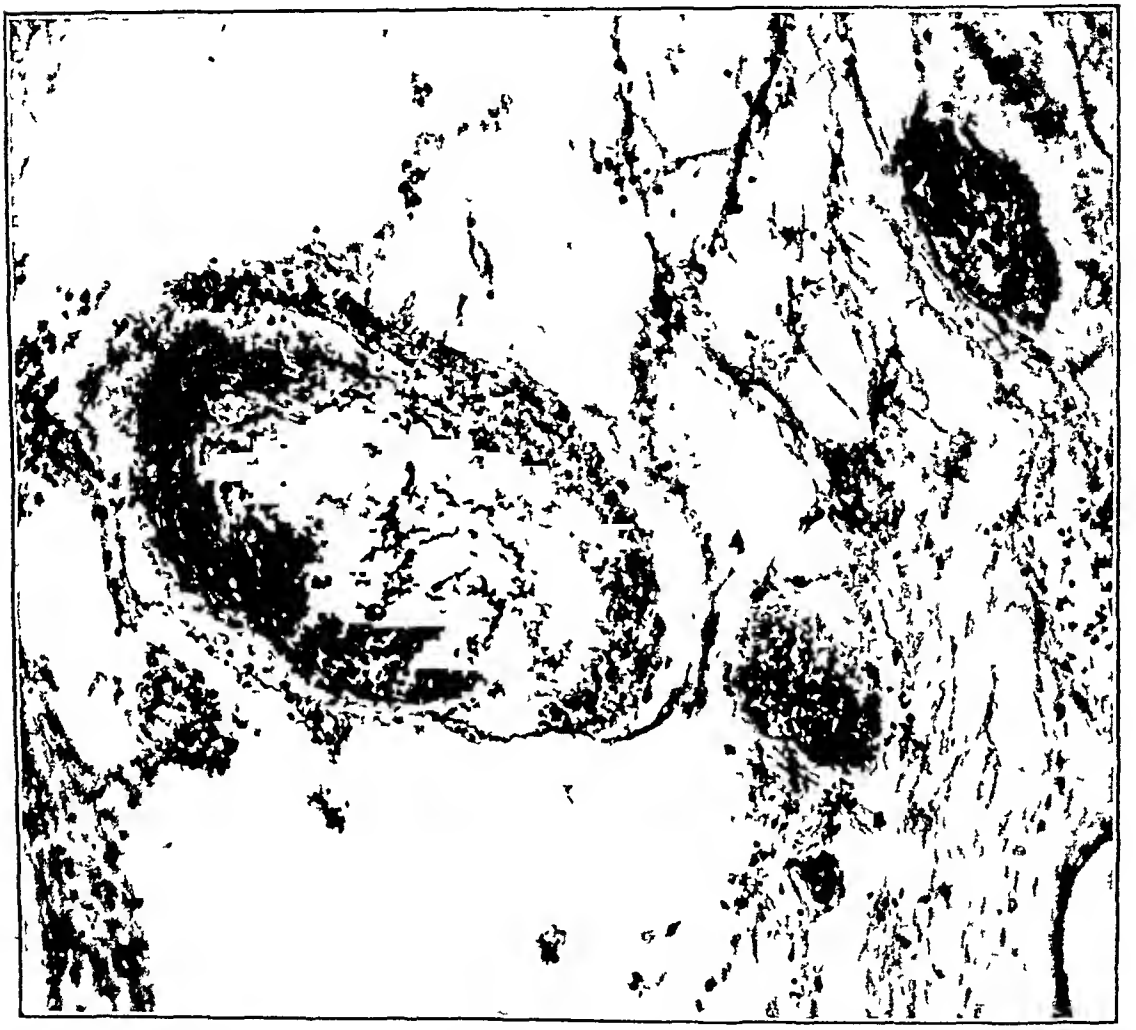

Fig 10 (case 3) —Complete destruction of nerve parenchyma in the vicinity of a thrombosed vein Cresyl violet stain, × 180

distended, containing two small blood clots only slightly adherent to the intima The wall of the vessel itself does not reveal visible structural alterations In addition, many veins and capillaries were tremendously distended, displaying varying stages of vasoparalysis Many of the smaller veins were engorged with blood and showed signs of stasis Their walls disclosed an increased permeability for red blood cells, with resultant diffusely scattered perivascular petechial hemorrhages

The changes in the nerve tissue proper consisted mainly of widely disseminated areas of hemorrhagic softening, involving chiefly the basal ganglia and the central white matter Some of the areas of softening were circumscribed and suggested a definite perivascular distribution In the central portion of these lesions one or more small veins displayed changes typical of vasothrombosis (fig 10) The sur-

rounding tissue showed all signs of an acute destruction of all the constituents of the nerve parenchyma, including the glial elements There were numerous small hemorrhages, chiefly perivascular in distribution While these lesions, as illustrated in figure 10, represented the most frequent type of tissue destruction, characterized by complete disintegration of all tissue elements without reactive glial changes, there were a few focal areas of glial proliferation, as illustrated in

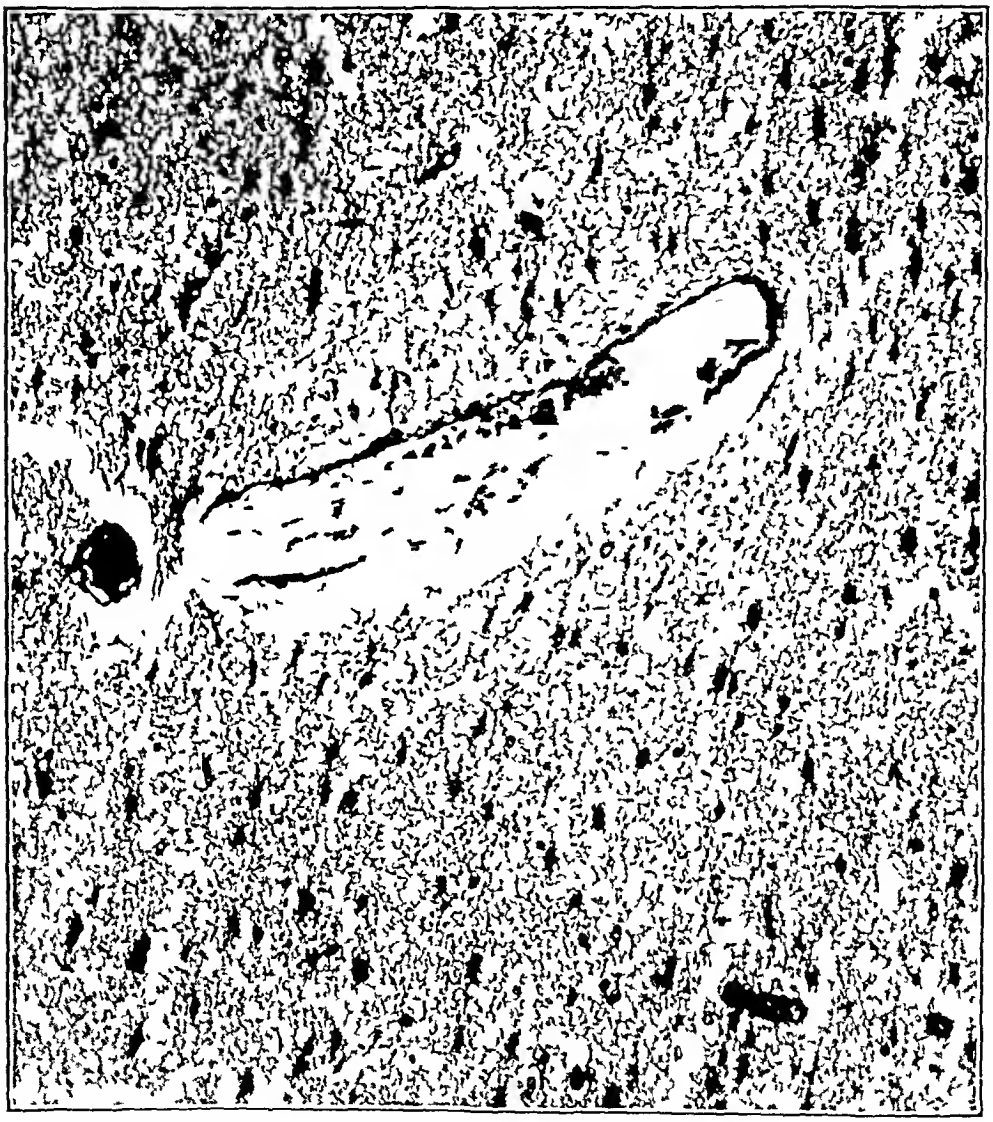

Fig 11 (case 3) —Focal area of sclerosis of the white matter in the vicinity of a thrombosed vein Note the diffuse proliferation of astrocytes Hematoxylin and eosin stain, × 180

figure 11 These focal lesions showed a diffuse proliferation of astrocytes, displaying an early stage of sclerosis and glial scar formation

The cortical gray matter was except for edema formation, fairly well preserved No signs of inflammation were seen The leptomeninges contained scattered red blood cells and a few macrophages The pial blood vessels were

maximally distended and engorged with blood, they were occasionally surrounded with large accumulations of extravasated blood Their walls showed no signs of structural lesions

SUMMARY OF PATHOLOGIC CHANGES

The microscopic picture in all 3 cases displayed circulatory disturbances of varying severity The earliest stage is illustrated by case 1, this was characterized by focal areas of perivascular transudation of serous fluid and concomitant liquefaction of the adjacent nerve parenchyma associated with regressive glial changes The absence of visible structural alterations in the blood vessels would seem to indicate that the alterations of the nerve tissue were mainly due to an increased permeability of the vessel wall for serous fluid A more advanced type of circulatory disturbance was found in case 2 The histologic alterations consisted in vasoparalysis of the smaller veins and capillaries with increased permeability of the vessel walls for red blood cells This resulted in numerous perivascular hemorrhages in the subcortical and central white matter In case 3 vasoparalysis of the smaller veins and capillaries was associated with vasothrombosis The most pertinent changes were characterized by formation of thrombi in the tremendously distended veins and capillaries, as illustrated in figures 8, 9, 10 and 11 The alterations of the nerve tissue proper, secondary to the circulatory disturbances, consisted in case 1 in perivenous tissue liquefaction, in case 2 in focal areas of extravasation of blood and in case 3 in focal areas of tissue necrosis contiguous to the occluded veins

It seems proper to conclude that the vascular alterations in all 3 cases are varieties of the same morbid process The differences in the morphologic features can probably best be explained by the differences in the duration and severity of the circulatory disturbances The formation of thrombi in case 3 might be interpreted as a late sequela of a prolonged state of vasoparalysis and was probably due to local slowing down of the circulation of the blood The clinical data seem to corroborate this conclusion In case 1 death occurred about forty-eight hours after the onset of the clinical symptoms, in case 2, after four days, and in case 3, after sixteen days

In all 3 cases the circulatory disturbances were predominant in the subcortical and central white matter The cortical gray matter was generally spared The discrepancy between the reactions of the gray and those of the white matter of the brain can best be explained by the differences in blood supply In a forthcoming paper the problem of selective involvement of the white matter will be discussed in greater detail The type of change and the distribution of lesions in the brain are influenced primarily by the local structure, and particularly by its vascular supply, which is rich in the cortical gray matter and poor in the white matter

According to Cobb, capillary counts revealed about 1,000 mm of capillary length per cubic millimeter of tissue in the middle layers of the cerebral cortex, as compared with about 200 mm of capillary length per cubic millimeter of tissue in the underlying white matter Of still greater importance is the difference in the arrangement and size of the vascular tree of the white and of the gray matter Whereas the cortical ribbon is supplied by a vascular system of the network type, formed by a tremendously dense net of capillaries, the vascular supply of white substance is composed chiefly of undivided vascular channels of considerable length, their anastomoses as compared with those of the cortex are scanty, wide meshed and more rectangular In studies on the cerebral vascular pattern, Alexander and Putnam [3] demonstrated these differences in a convincing manner The great majority of the larger vessels of the white matter are veins With serial sections, Alexander and Putnam were able to demonstrate that these veins drain into the vena striae terminalis and thence into the vena magna of Galen

The vascular alterations described as vasoparalysis and vasothrombosis involve chiefly the veins and capillaries of the white matter Stasis and, eventually, immobilization of blood flow appear to constitute the main factor It is obvious that the effects of retarded circulation are more apt to be observed in the poorly vascularized white matter than in the gray substance, which is richly supplied by an arborized vascular network The absence of rich anastomoses in the white matter would facilitate the detrimental effects of stasis and would explain the selective vulnerability of the white matter for circulatory disturbances

GENERAL COMMENT

It is surprising how few histologic studies concerned with this type of alterations in the brain are available in the literature In the summer of 1923 Brown, working at the Children's Hospital in Boston, observed 6 cases of rapidly fatal disease in children In 5 of the cases necropsy revealed "intense edema and congestion of the brain" In the summer of 1929, Symmers, working at Bellevue Hospital, in New York, observed 5 cases in which the clinical and anatomic changes were identical with those encountered in Boston Brown and Symmers [4] reported their observations as cases of "acute serous encephalitis" Unfortunately, the histologic studies were incomplete, which makes difficult a comparison with the lesions observed in the present cases "Engorgement of the blood vessels of the brain, perivascular and pericellular edema" are mentioned as the most constant changes In spite of the fact that

3 Alexander, L, and Putnam, T J Pathological Alterations of Cerebral Vascular Patterns, A Research Nerv & Ment Dis, Proc **18** 471, 1938

4 Brown, C L, and Symmers, D Acute Serous Encephalitis A Newly Recognized Disease of Children, Am J Dis Child **29** 174 (Feb) 1925

no inflammatory changes were observed, the authors apparently came to the conclusion that "the disease belongs to the same general category with the so-called encephalitis lethargica" Needless to say, the clinical picture, as well as the cerebral alterations in my cases (and in cases reported by Brown and Symmers) does not warrant the assumption of any similarity with encephalitis lethargica On the basis of my own observations, it seems proper to conclude that the condition represents a special form of damage to the brain secondary to reversible vascular disturbances characteristic of vasoparalysis and vasothrombosis

Marburg and Casamajor [5] reported 2 cases in which extensive areas of destruction of the brain corresponding to the drainage areas of the great vein of Galen and the superior longitudinal sinus were found to be caused by venous thrombosis The pathologic process, as well as the clinical picture, does not disclose a relationship to the present cases

SUMMARY

In 3 illustrative cases of a rapidly fatal disease in early childhood, attended by symptoms of acute encephalitis, necropsy revealed circulatory disturbances characteristic of vasoparalysis and vasothrombosis

In all 3 cases there were no signs of inflammation The most striking observations were different phases of vascular alteration

The earliest manifestations of the pathologic process were found in case 1 and consisted in focal areas of perivascular transudation of serous fluid and concomitant liquefaction of the adjacent nerve parenchyma Since no lesions could be seen in the walls of the vessels, the pathologic process was interpreted as due to increased permeability of the vessel for serous fluid

In case 2 a more advanced stage of vasoparalysis was displayed with increased permeability of the vessel wall for red blood cells, resulting in perivascular hemorrhages in the white matter

The changes in case 3 were characterized by thrombotic occlusion of the smaller veins and were interpreted as late sequelae of a prolonged state of vasoparalysis

The pathologic changes in the 3 cases appear to represent three phases of the same morbid process The difference in their morphologic features can probably best be explained by the difference in the duration and severity of the circulatory disturbance

Regional peculiarities of vascularization appear to be responsible for the greater vulnerability of the white substance and the relative preservation of the cortex

Cincinnati General Hospital

5 Marburg, O, and Casamajor, L Phlebostasis and Phlebothrombosis of the Brain in the Newborn and Early Childhood, Arch Neurol & Psychiat **52** 170 (Sept) 1944

DIVERGENCE PARALYSIS ASSOCIATED WITH TUMOR OF THE BRAIN

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DIVERGENCE paralysis associated with cerebral tumor has been reported in only 5 cases, 2 of which were verified Straub [1] reported the case of a 20 year old woman with bilateral papilledema, involvement of the left trigeminal, facial and acoustic nerves and bilateral nystagmus The author's diagnosis was "tumor" of the middle fossa Howard [2] described the case of a woman aged 71 who had had a carcinoma of the breast removed five years previously She complained of diplopia for two months prior to the examination, which revealed divergence paralysis Multiple areas of destruction of the bony cranial vault and the sella turcica were observed in the roentgenograms The diagnosis was "metastasis of the carcinoma to the supposed divergence center" Holden [3] mentioned seeing divergence paralysis in a case of "mid-brain tumor" but gave no clinical data These 3 cases were not verified by operation or necropsy Lippmann [4] recently described the case of a youth aged 20 who had had divergence paralysis for about two years with cerebellar signs, especially on the left side At operation a cerebellar tumor was found and partly removed, but the patient died Bender and one of us (N S) [5] reported a case of a small vascular tumor in the pons Divergence paralysis was the chief complaint during life

We report 4 additional proved cases of tumor of the posterior fossa 2 of cerebellar tumors and 2 of acoustic neuromas Divergence paralysis probably occurs more frequently than is indicated in the literature A review of a report of a large series of tumors of the posterior fossa

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Dr I S Wechsler, Chief of the Neuropsychiatric Service of the Mount Sinai Hospital, permitted us to use the records of the hospital

From the Division of Neuropsychiatry, Montefiore Hospital, and the Department of Neurology Columbia University College of Physicians and Surgeons

1 Straub, M Ueber Lahmung der Divergenz, Centralbl f prakt Augenh **21** 8, 1897

2 Howard, H J Divergence Paralysis, Am J Ophth **14** 736, 1931

3 Holden, W A The Ocular Manifestations of Epidemic Encephalitis, Arch Ophth **50** 101, 1921

4 Lippmann, O Paralysis of Divergence Due to Cerebellar Tumor, Arch Ophth **31** 299 (April) 1944

5 Bender, M B, and Savitsky, N Paralysis of Divergence, Arch Ophth **23** 1046 (May) 1940

(Cushing,[6] Henschen[7] and Olsen and Horrax[8]) reveals the occasional mention of diplopia with no evident ocular palsies or impairment of conjugate gaze Precise analyses of these unclear cases of diplopia are usually lacking The present investigation leads to the conclusion that more careful study of some of these cases would probably have indicated the presence of divergence paralysis This divergence paralysis can easily be detected with the red glass test There was no evidence of weakness or paralysis of the external rectus muscle in any of the present cases

REPORT OF CASES

CASE 1—A woman aged 22, single, was admitted to the Mount Sinai Hospital because of pain in the back of the head and vomiting of six months' duration The vomiting was projectile and had persisted from the onset to about two months prior to her admission Diplopia on looking at a distance appeared three weeks before she entered the hospital During the week preceding her admission vomiting reappeared, and the pain in the neck had increased in severity

On examination a bony protrusion was palpated over the right occipital bone. The gait was broad based, with a tendency to veer to the right There was slight tilting of the head to the right, and the neck was held stiffly Bilateral papilledema with hemorrhages and exudates, lateral nystagmus and occasional horizontal nystagmus were observed There were past pointing and drift of the right upper extremity

Lumbar puncture revealed a slightly xanthochromic fluid, with an initial pressure of 220 mm of water and a total protein content of 33 mg per hundred cubic centimeters Roentgenographic study of the skull was disturbing in that there seemed to be a large bony defect in the floor of the middle fossa Because of this the nasopharynx was examined for a tumor, but none was found Ventriculographic examination revealed bilateral internal hydrocephalus without a shift A suboccipital craniotomy was carried out, and a large cyst was encountered in the right cerebellar lobe and extending into the tonsil, which was herniated through the foramen magnum The arch of the atlas was removed, and at the tip of the tonsil a tumor was found which formed the mural nodule of the cyst The diagnosis was hemangioendotheliomatous meningioma, and removal was complete

The postoperative course was marked by slight paresthesias in the left hand The patient improved but showed slight papilledema at the time of her discharge, on March 11, 1943 The diplopia and the divergence paralysis disappeared soon after the operation

CASE 2—A woman aged 54 was admitted to the Mount Sinai Hospital on Oct 21, 1943, with a history of nausea, vomiting, headaches of about three weeks' duration and buzzing in the left ear since September 1941 During August

6 Cushing, H Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle, Philadelphia W B Saunders Company, 1917, p 165

7 Henschen, F Ueber Geschwulste der hinteren Schädelgrube, insbesondere des Kleinhirnbrückenwinkels, Jena, G Fischer, 1910

8 Olsen, A, and Horrax, G The Symptomatology of Acoustic Neuromas, with Special Reference to Atypical Features J Neurosurg 1 371, 1944

1941 she had had transient "weak spells" In February 1943 blurring of vision was noted and she began to see double at a distance

On examination there were bilateral papilledema, lateral nystagmus on looking to the right and left and drift of the right upper extremity Hearing was impaired on the left side Divergence paralysis was demonstrated with the red glass test There was no evidence of weakness of the external rectus muscle The caloric test indicated no response on the left side The electroencephalographic pattern was normal A ventriculogram demonstrated symmetric dilatation of the ventricular system with cutting off of the tip of the left temporal horn

At operation a perineural fibroblastoma was removed from the left cerebellopontile angle The divergence paralysis disappeared after the operation, and the patient was discharged eight weeks after admission

CASE 3—A man aged 51 first complained of double vision while playing golf in August 1943 He began to have attacks of pain in the back of the neck with radiation to the left temple several times a day During the night before he was examined he had sharp pain on the top of the head

Examination, on Oct 19, 1943, showed bilateral papilledema, clockwise rotatory nystagmus on looking to the left, divergence paralysis, a diminished left corneal reflex and diminished bone conduction on the left side Bone conduction was better than air conduction bilaterally There was an old perforation of the left ear drum The patient had a history of inability to hear with the left ear for fifteen years

On Nov 2, 1943 there was increasing bilateral papilledema with hemorrhages and exudates On November 12 there were spontaneous outward pass pointing to the left, concentric constriction of the visual fields with enlarged blindspots, bilateral ataxia in the heel to knee test, more marked on the right, and hyperreflexia with a positive Babinski sign on the left side There was still bilateral papilledema with rotatory nystagmus on looking to the left Hearing was almost entirely lost on the left side, and caloric responses were absent on that side Divergence paralysis persisted, with no evidence of involvement of either external rectus muscle

At operation, on November 23, an acoustic neuroma was removed on the left side Transitory palsy of the sixth nerve and weakness of the lower part of the face appeared on that side after operation Slight ataxia in the heel to knee test and a Babinski sign were present on the left side The divergence paralysis disappeared, and the hemorrhages in the retinas cleared up soon after the operation On Jan 24, 1944 there were no complaints except for slight dull headache

CASE 4—A white man aged 54 was admitted to the Montefiore Hospital on July 11, 1945, complaining of inability to stand or walk for three months Headaches and double vision appeared during June 1941 About that time he first noted that his gait was unsteady Several days later frontal and retro-orbital headaches appeared, which were intensified on his lying down and were somewhat relieved by his tilting his head to the right He also complained of occipital and nuchal pain A week later he noticed slight weakness of the left hand and double vision in all directions.

He was admitted to the Mount Sinai Hospital on July 18, 1941 Examination revealed a deformity of the occipital region of the skull The occiput was flattened The gait was wide based, with a tendency to veer to the right Bilateral dysdiadokokinesis, spontaneous pass pointing to the left, slight ataxia of the left lower limb, bilateral papilledema, bilateral diminution of hearing,

nystagmus in all directions and a slightly more active knee jerk on the left side were observed There were no palsies of the external ocular muscles

Electroencephalographic study suggested an expanding lesion in the posterior fossa Ventriculographic examination showed symmetric dilatation of the lateral ventricles Operation exposed a large vascular tumor occupying the vermis and the adjacent portion of both cerebellar lobes, especially on the right, with projection of the tumor into the spinal cord Because of the extreme vascularity, radical removal was not attempted, and only a biopsy was done

The clinical picture at present consists in bilateral cerebellar signs in the upper and lower limbs, nystagmus, cerebellar speech, slight hyperreflexia and a positive Babinski sign on the right side, inconstant divergence paresis and bilateral papilledema There is no evidence of weakness of the external rectus muscle

In a case previously reported by 1 of us (N S),[5] a tumor was found within the brain stem It was assumed that the region of the divergence center had been involved by the neoplasm In the 4 cases reported in this paper and in Lippmann's case there was no clinical evidence of disease of the brain stem In each of the present 4 cases a tumor of the posterior fossa was found at operation We have not yet encountered a supratentorial tumor with divergence paralysis, though false localizing signs in the brain stem have been reported with such tumors (Nielsen and Hollenbeck[9] and Pichler[10]) We have thus far not found divergence paralysis in cases of increased intracranial pressure without tumor or in cases of intraventricular tumors In the absence of any available anatomic studies of the brain stem in such cases, a definite opinion regarding the pathologic changes in the pons cannot be given

CONCLUSIONS AND SUMMARY

We add 4 cases of divergence paralysis associated with cerebral tumor to the 5 cases recorded in the literature

Cranial exploration in all the cases revealed a tumor of the posterior fossa

We believe this divergence paralysis is the result of involvement of the divergence center in the brain stem in some way

The divergence paralysis may be inconstant

The divergence paralysis disappeared in the 3 cases in which the tumor was successfully removed

1882 Grand Concourse (57)

9 Nielsen, J M, and Hollenbeck, A E A Case of False Localizing Signs of Cerebral Neoplasm, Bull Los Angeles Neurol Soc **5** 124, 1940

10 Pichler, E Zur Frage der Bedingtheit irrefuhrender Symptome bei Grosshirntumoren, Arch f Psychiat **110**:75, 1939

COMBAT NEUROSES

Development of Combat Exhaustion

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IN World War II the neuroses which result from combat have been designated as "combat exhaustion" This terminology implies two fundamental things First, these neuroses are due primarily to combat, and, second, they develop after a period of combat sufficiently long to produce a significant degree of exhaustion [1] Through misunderstanding many people use the term indiscriminately, and confusion has arisen, they include under this head the neuroses which develop during the first few days of combat, and even the disorders of behavior of men who have never experienced actual combat The usefulness of this term in distinguishing the more stable and willing from the unstable and unwilling personalities is thereby lost This is unfortunate, since a substantial percentage of men are of the former type and have broken down under conditions of continuous long and severe stress which infrequently, if ever, obtained before The number of early breakdowns has been reduced by a better selection of personnel on induction, followed by the further "weeding out" of potentially weak and unwilling persons during basic training and in battle simulation exercises prior to actual combat

The present paper is a description of combat neuroses, in an attempt to clarify the syndrome or syndromes of combat exhaustion and their relationship to neuroses in general Although emphasis will be placed on one unit and the men in it who remained longest in combat, observations on many other units will be included, and the problem in general will be considered For orientation, the behavior of the men during the period immediately prior to combat will be discussed This section will be followed by a description of, first, the behavior of soldiers in combat and, second, the changes in behavior which these men undergo during the first week or so after evacuation from combat

1 Hereafter in this paper the designation "combat exhaustion" implies that these two factors are present

BEHAVIOR DURING THE PERIOD OF "ALERT" PRIOR TO COMBAT

The duration of this period was no doubt variable, but for the unit under observation it was approximately eighty days

Most men exhibited feelings of insecurity and irritability First, there was an increase in difficulties concerned with domestic life and courtship arising from failure of people at home to respond to the soldier's increasing demands for declarations of love and fidelity Secondly, many men who had seldom or never gone to church or sought religious solace became very religious and exhibited improved moral behavior in preparation for the possibility of death Third, the soldier frequently expressed the sentiment, by word or in letters, that, although his comrades might become casualties, he would come through alive In contrast to this major group, a few men, although well disciplined before, assumed a "devil may care" attitude toward Army regulations and superior officers and became morally delinquent This attitude is expressed in the words "The worst that they can do is to shoot me, and I'm going to be killed anyway"

During this period there was an increase in the number of functional complaints, chiefly dyspnea, palpitation, weakness, abdominal pain, vomiting and backache Many men were hospitalized for these disturbances and were not returned to the unit There was also an increase in the number of self-inflicted wounds, which resulted in a further loss of personnel Lastly, malingering, either through self injury or through a display of physical inaptitude during preinvasion amphibious exercises, was responsible for the loss of a few men from the unit The total loss of man power through the aforementioned means was not great and represented the final screening of men unfit for combat

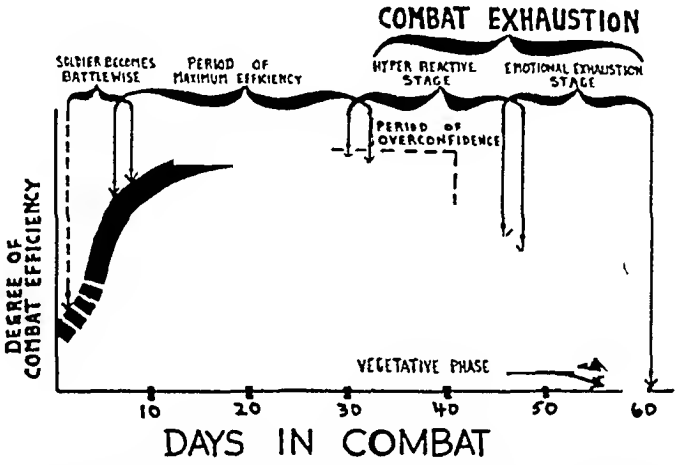
Obvious generalized anxiety was first noted when the unit was told that it would take part in the assault on the Continent During the ensuing months, however, the men became adjusted to the role they were to play, their anxieties subsided and were not observed again until embarkation During the crossing of the Channel generalized restlessness was in evidence, but there were no actual displays of fear until the men went "over the side" to assault craft in a rough sea prior to H-hour The men then crowded toward the rear of the craft in search of safety against striking a floating mine or an underwater obstacle From that point on life was to consist of a series of dangerous situations, each accompanied with new anxieties or fears which had to be overcome

BEHAVIOR DURING COMBAT

Development of Combat Exhaustion—During the first few days of combat the men were in a constant state of fluctuating fear They had

urinary frequency and urgency, intense thirst, anorexia, and even a fear of eating, a fear of being left alone or of exposing themselves, even to defecate, and an increase in sweating During acute incidents, palpitation, an increase in sweating, vasomotor instability and the overt signs of fear, such as tremulousness, became more or less universal Many men became selfish to the point that they took food, blankets, entrenching tools and similar articles from others for their own use This soon stopped, however, when they realized that individual survival was dependent on survival of the group, and cooperation, to the point of self deprivation, continued throughout the ensuing period of combat

Gradually the men became adapted to the existing conditions of battle They became familiar with the sounds of their own, as contrasted with the enemy's artillery and automatic small arms weapons From the sound they could determine the caliber of artillery fire and



Graphic portrayal of the relation of stress and the development of combat exhaustion to the combat efficiency (heavy black line) of the average soldier

how close the projectiles would fall, thereby knowing when to "hit the dirt" Without being conscious of it, they chose paths of approach which afforded concealment and cover, and they constantly watched for snipers in trees and hedges Smoke and fire discipline at night became automatic, and the soldier was always well oriented to his own and the enemy's strength and position These significant, yet subtle, changes, as well as many others, constitute the state of "battle wiseness," without which the soldier does not survive to become efficient in combat Concurrently, the physiologic reactions to danger, referred to before, became modified or controlled to the point that they no longer hindered the soldier in combat Short periods of overt anxiety appeared from time to time after this in the face of unexpected dangers or developments, e g, the use of "new weapons" by the enemy, but these rarely

developed to the stage that was harmful, and they were soon brought under control again

The large majority of men achieved adequate adjustment in approximately five to seven days By that time they had become efficient in combat and could rightfully be considered "battle wise" Further, and slow, improvement followed, peak efficiency as a combat soldier being reached about D plus 21 day This held for approximately one week longer, the entire period of maximum efficiency in battle lasting about three weeks The majority of men then showed a gradual and steady decline in efficiency, attended by the development of abnormal psychologic and emotional reactions In a few overconfident ones, however, high efficiency in combat was prolonged for a short period These men felt that they were immune from danger, they exposed themselves unnecessarily, and they were especially aggressive in battle Their casualties were high, and the few who were not killed soon adopted the general behavior of the group This will be described now

The first symptom of combat exhaustion made its appearance at about D plus 25 to D plus 30 day in most soldiers This was an abnormal fatigability, which could no longer be relieved by periods of rest up to forty-eight hours The fear reactions, so noticeable early in combat, and so successfully controlled during the period of high efficiency in battle, reappeared more frequently and were quelled with less success Unconsciously, the soldier lost confidence in himself This was clearly shown in his reactions toward various battle stimuli He began to lose the fine points of discrimination in which he had prided himself He no longer could tell the difference between friendly and enemy artillery and mortar fire and referred to all as the fabulous "eighty-eight"

To all these stimuli his reactions became excessive, often to the point that they were harmful He became overcautious, he stayed close by or in his slit trench whenever possible, he walked rather than rode in a vehicle, so that he would be able to get to cover more readily, and he became a "follower" rather than a leader Sleeplessness became evident early and persisted despite his mounting exhaustion If he slept at all, it was during the hours of daylight, because of a greater feeling of insecurity during the hours of darkness A feeling of insecurity was also shown by the fact that he repeatedly wanted to "know the situation," i e, the disposition of the enemy, the availability of supporting troops and the Allied success in dealing with the enemy Some degree of irritability also made its appearance This was shown in mild form by his statements that the campaign was being run poorly and that things in general were not working out as smoothly as they had once The blame for this was always placed on other units,

which he felt were not performing their mission, or on some higher headquarters, which did not "know the score" In more severe form, the irritability consisted in "blowing his top" over matters which at one time would have left him unconcerned Restlessness was usually present and often became so extreme that he had difficulty remaining in his slit trench even when under fire Anxiety concerning himself, both directly and remotely, became progressively in evidence during this period, the facies associated with fear and anxiety became progressively more apparent and persistent, and tremulousness came to be ever present

As the casualties mounted and his old friends became conspicuous by their absence, he was increasingly aware of his dwindling chances of survival, and a feeling of hopelessness became evident This was expressed by such remarks as "I guess I'll get mine tomorrow", "We [meaning the unit] can't keep going like this", "They'll wipe us out sooner or later," and "I might as well get hit now and get it over with" This evident hopelessness, however, was transient rather than fixed, as indicated by his recognition that should the type of warfare change from static to fluid there would be a chance for survival

The type of warfare did not alter, and the pace of advance remained the same During the period of D plus 40 to D plus 45 day a group of symptoms which will be referred to collectively as "emotional exhaustion" first made their appearance These are characterized by a general slowing of mental processes and apathy, in contrast to the hyperactivity and marked anxiety which had been present before The men became resigned to the state in which they found themselves, and as far as they were concerned the situation was one of absolute hopelessness They saw no means of overcoming or getting beyond the state of things, only that it was meant for them to "sweat it out" The thought and hope of surviving combat were now foreign, one thing to them was certain, they would be killed Should they be lucky, they would be merely wounded The influence and reassurance of capable and understanding officers and noncommissioned officers failed now to arouse these soldiers from their feeling of hopelessness

Symptoms which had been developing insidiously now became evident The soldier was slow witted, he was slow to comprehend simple orders, directions and technics, and he failed to perform even life-saving measures, such as digging in quickly Memory defects became so extreme that he could not be counted on to relay a verbal order There was also present a definite lack of concentration on whatever task was at hand, and the man remained preoccupied for the most part with thoughts of home, the absolute hopelessness of the situation and death This constant dwelling on death did not indicate a state of fear but,

rather, a certainty that it would occur The anxious state, together with the tremulousness and generalized hyperactivity, was replaced gradually by an emotionless expression, lassitude and listlessness

Some men exhibiting the picture just described were not evacuated, and all such symptoms became intensified to the point that the soldier became practically nonreactive both physically and emotionally He could then best be described as one leading a vegetative existence His facial expression was one of complete apathy a nonsmiling, rigid-faced person with lusterless eyes His body was seemingly helpless, movements being performed with an effort The soldier was in a semistuporous state, difficult to arouse from his reverie, he remained almost constantly in or near his slit trench, and during acute actions he took little or no part, trembling constantly

A soldier with combat exhaustion usually continued in battle until he was exposed to an acute and severe "incident," such as a "near miss" from artillery or mortar fire or a heavy artillery barrage In many instances a close friend was often killed before "his very eyes" This usually provoked a violent emotional explosion, and the soldier became disoriented and confused Often he ran about wildly and aimlessly, with a total disregard for danger, rolled on the ground and cried convulsively For this episode and the succeeding evacuation to an aid station he was usually amnesic, totally or in part In some instances he remained stuporous, prostrate, amnesic and unable to talk or hear clearly for days, and in this state he arrived at a general hospital Noises which were associated with danger, i e, airplanes and gunfire provoked violent trembling and agitation This behavior sometimes lasted for weeks, being temporarily relieved by sodium amytal or pentothal given intravenously, at which time the soldier's past and combat history could be readily elicited With the end of this short narcosis he returned to the stuporous, confused, amnesic state which existed before

Other Psychologic Reactions Which Necessitated Evacuation From Combat—As might be expected, a number of men failed to adjust themselves during the first or the succeeding weeks of combat These men fell into several groups One group became panicky or terror stricken at the first sign of danger Even a minor small arms skirmish with the enemy, a single artillery barrage, bombing or strafing, a night attack, or a counterattack caused them to become suddenly disoriented, confused and amnesic They ran around wildly, even toward the enemy's line or the artillery impact area Some fell to the ground, clawing the earth, or, finding a slit trench, remained there, crying and trembling, impossible to control A short period of sedation in the

rear and reassurance quickly quieted most of them, and a number returned to combat Many of them, however, had to be evacuated from the combat area, where they improved rapidly to an apparently normal state when reassured that they need not return to combat Their tolerance for danger remained low, and they displayed fear or anxiety when enemy, or even friendly, aircraft were overhead or during periods when rumors were rampant In a second, and smaller, group of men conversion symptoms developed, during this early period of combat, such as paralysis of an arm or visual defects The prognosis for their recovery from the immediate hysterical manifestation was usually good, but for a return to combat it was very poor

Few somatic complaints were noted during the first few days of combat These became more common after two or three weeks of combat and consisted primarily of abdominal pain and vomiting, backache and headaches More often than not, when incapacitated by these symptoms, either the soldier had suffered from the same trouble in civilian life, or there was some anatomic basis for his trouble In veteran soldiers these somatic complaints, especially abdominal pain, were probably more common Yet they were seldom disabling, and they attended the anxiety and psychologic symptoms of combat exhaustion present in most troops of the unit under consideration after thirty days of combat As a rule these soldiers seemed to have insight into their troubles, and reassurance usually satisfied them A few veteran soldiers had severe abdominal pain and vomiting but attributed this to the C or K rations which they had existed on for weeks, and even months [2]

Conversion hysterical symptoms were also unusual in the veteran combat soldier One case of foot drop, 1 case of gross paralysis of a leg, several cases of aphonia and several of deafness are remembered It was the impression that previous organic disease was simulated in most of these cases Amnesia was seen in veteran combat troops rarely, if at all, except in men who were confused and emotionally exhausted or in men suffering a blast concussion

CHANGES IN BEHAVIOR WHICH OCCURRED DURING THE FIRST WEEK AFTER EVACUATION FROM COMBAT

Men who had broken down early in combat or who had never adjusted to combat usually appeared very anxious or fearful Their

2 These diets are recognized as having low thiamine contents, and it has been recommended that they be supplemented with foods rich in vitamins if consumed for longer than five days ("Messing in the ETO," prepared by the Office of Chief Quartermaster, Headquarters, Services of Supply, European Theater of Operations of the United States Army, February 1944)

anxiety appeared superficial, and diversion or the assurance that they would not be returned to combat quickly quelled their uneasiness The few calm persons in this group were greatly disturbed by threats of combat The few with hysterical paralysis, deafness and similar symptoms remained quite unperturbed

By far the majority of patients were victims of combat exhaustion All these men were tense, sleepless, irritable and fearful of noises simulating combat, and almost all suffered from dreams of combat Most complained of various somatic symptoms, but these were rarely incapacitating Two subgroups were readily identified, although most of the patients exhibited symptoms of both The patients in one group were very anxious, hyperactive, both mentally and physically, and restless Some were emotionally unstable to the point that they became angry or cried at the slightest provocation or became irritated and uncompromising toward their best friends for similar trivial reasons These men represented the early, or beginning, phase of combat exhaustion, i e, the hyperreactive phase The patients in the second group were dull and listless, they were preoccupied more or less of the time, were retarded mentally and physically and in some instances appeared apathetic These men represented the later phase of combat exhaustion, i e, the phase of emotional exhaustion Only a few patients remained semistuporous, prostrate, amnesic and extremely agitated by sudden noises In short, most men exhibited the essential features of combat exhaustion The anxiety, retardation and other psychologic changes had all lessened in intensity, probably as a result of the narcosis therapy which they had received forward and the relative quiet and security of the hospital One feature was noteworthy In this period of seven to ten days many of the very retarded, preoccupied and apathetic patients changed to appear anxious and showed definite evidences of increasing brightness, increasing ability to concentrate, increasing motor activity and diminishing preoccupation At this time also, a number of men began to show evidence of mild depression of mood

COMMENT

It is necessary for the reader to understand clearly that the foregoing description applies to the average soldier in the unit under observation Other factors being equal, it is recognized that individual tolerance for battle stress varies Combat exhaustion may appear in as few as fifteen or twenty days or in as many as forty or fifty days instead of in approximately thirty days, as it did in the majority of men One thing alone seems to be certain Practically all infantry soldiers suffer from a neurotic reaction eventually if they are subjected to the stress of modern combat continuously and long enough True as this

statement appears to be, an occasional soldier seems capable of withstanding combat for an inordinate length of time Perhaps less than 2 per cent (as judged by numerous conversations with veteran soldiers) fall into this class [3] No personality type dominates this small, "abnormal," group, but it is interesting that aggressive psychopathic personalities, who were poorly disciplined before combat, stand out

The fact that some men continued in combat for one hundred to one hundred and fifteen days, and even longer, is likely to be misleading Near D plus 55 day static warfare was replaced by fluid warfare The Allied forces broke through the enemy's lines, and many units broke out into the open and made rapid and satisfactory progress Under these conditions many men on the verge of breakdown appeared to improve, or merely carried on temporarily When the enemy's resistance became organized again, especially when these men were subjected to heavy artillery fire and were "pinned down," all symptoms of combat exhaustion flared up, and the long-awaited breakdown followed The fact that the exploitation of the break through was accomplished with a maximum physical effort and that the subsequent period, when units were "pinned down," was accompanied with a minimum physical effort, indicates the relative unimportance of factors of physical stress in the production of combat exhaustion

Another extremely variable factor, possible of being misleading, is the stress of combat itself In the Normandy campaign, from D-Day until the break through, this stress was continuous and severe Rests were infrequent and usually for no longer than one day Particularly severe was the last part of the campaign Each hedgerow had to be fought for and "sweat out" Casualties occurred daily at a rate which convinced even the most confident soldier that death or mutilation was certain unless the type of warfare changed In the unit under consideration the casualty rate was about average for the combat infantry units in that campaign Several other units were less fortunate and had casualty rates much higher In these units the symptoms of combat exhaustion developed much more quickly In another unit with a lower than average casualty rate fewer cases of breakdown were seen, and these developed only after a much longer period of combat

The character and development of combat exhaustion also varied somewhat with the intensity of the stress The term "stress" is used here in a general way In practice, however, the casualty rate and

3 This seemed true when this paper was written, in November 1944 Since then we have concluded that all normal men eventually suffer combat exhaustion in prolonged continuous and severe combat The exceptions to this rule are psychotic soldiers, and a number of examples of this have been observed

its implications were by far the most important factors In units with a higher or lower than average casualty rate, the stages of behavior through which the combat soldier passed were likely to be less distinct In the former, the soldier might never adjust himself to combat, and in a period of from fourteen to twenty-one days there might develop a neurosis comparable to the hyperactive stage of combat exhaustion without his first becoming "battle wise" or efficient in combat In the latter, the stage of anxiety, or hyperreactivity, was frequently passed over without being noticed, emotional exhaustion developing insidiously Here, again, it should be clear that the response of different soldiers to the same stimulus was not always the same Hence, great individual variations within units were noted

Most men who suffered from a neurosis (probably about 70 per cent) were evacuated from combat immediately after an acute "incident" Early in combat, small arms fire, a single aircraft strafing or a short artillery barrage constituted an acute incident In the veteran soldier a much stronger stimulus was usually required, e g , a heavy artillery barrage or a near miss from artillery fire or mortar shell or bomb The mechanism by which these "acute incidents" precipitated neurotic reactions is not clear, but the following explanation, although crude, is offered

In many cases the stimulus was psychologic and should be considered as an acute exacerbation of battle stress, a terrorizing experience Men so affected were usually dazed, confused and uncontrollable but were seldom unconscious In a smaller number of men real concussion probably occurred, resulting either in physiologic or in anatomic damage to the nervous system and its exteroceptive nerve endings, as well as to other parts of the body Men so affected usually heard the concussing blast and sensed vaguely that they had been blown through space For subsequent events they were completely amnesic or dazed for a varying period, and often it was reported that they had been unconscious They recovered consciousness at an aid station or farther back of the line and discovered that their hearing was impaired, that there was a constant buzzing in one or both ears or that they had a headache and were dizzy Many had bled from the ears, nose and/or mouth Pains in the chest and other symptoms due to blast might be present Frequently one or both tympanic membranes had been ruptured Recovery from the effects of blast was slow, but as this occurred symptoms of combat exhaustion usually became increasingly evident It was possible usually to determine that the soldier had suffered from some symptoms of combat exhaustion before the blast, and the evidence was strong that, in addition to physiologic and possible anatomic effects,

psychologic trauma had also occurred and had intensified the neurosis In most instances the symptoms of blast referable to the nervous system cleared in one to three or four weeks In a few cases, however, these symptoms persisted for as long as twelve months, possibly in those instances there was anatomic damage to the nervous system It is interesting that some men with symptoms of severe concussion due to blast exhibited no evidences of combat exhaustion

The recognition and evaluation of combat exhaustion may be difficult by virtue of the changes which occur in its symptoms and its apparent similarity at times to normal fear reactions The first reaction of the average soldier to combat was one of anxiety and fear This became controlled in the "battle-wise" soldier Later, the soldier appeared to lose this ability to control his emotions, and anxiety reappeared in a somewhat similar form The violence of these emotional and physical reactions gradually diminished, and a general slowing down of all mental and physical processes, not accompanied as a rule with mood depression, developed The final picture was one of apathy, with pronounced physical and mental retardation This we have chosen to refer to as emotional exhaustion, since the mood response to ordinary stimuli is weakened or absent There is a definite similarity of this picture to that of schizophrenia, and the condition of many of these patients was so diagnosed before they arrived at the general hospital In the hospital a slow regression of symptoms occurred The patient became more active mentally and physically, and his mood response to ordinary stimuli increased in intensity In most patients the anxiety reappeared, but in many a definite, but mild, depression became evident As the neurosis became more chronic, mood depressions became more frequent, but rarely were they severe

Despite this changing picture, the breakdowns early in combat and the early manifestations of combat exhaustion are usually recognized with ease This statement applies also to the extremely retarded and apathetic soldier Unfortunately, in a significant number of men symptoms develop so insidiously that they are not evacuated until after an "acute incident" By the time these men arrive at a general hospital, either spontaneously or as the result of receiving narcosis therapy forward, they have recovered their composure and appear slightly anxious Frequently they are without insight into the nature of their condition Careful observations reveal, however, that they are retarded, preoccupied, lacking in ability to concentrate and in other ways very ill Too often this state is overlooked entirely or is mistaken for a constitutional defect The results of adequate physical therapy and a knowledge of the man's combat history are sufficient in most instances to correct this impression

SUMMARY

The behavior of combat soldiers who took part in the assault on Normandy is described and discussed The development and characterization of combat exhaustion are outlined, and the relation of this condition to neuroses in general and to blast concussion is noted The effect of the severity and duration of combat stress on the symptoms and their mode of development are emphasized

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NEUROFIBROMATOSIS WITH DEFECT IN WALL OF ORBIT

Report of Five Cases

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MINNEAPOLIS

SINCE von Recklinghausen described neurofibromatosis in 1882 there has been a radical change in the concept of this disease It is now well recognized that the cutaneous tumors and the pigmentation, as described by von Recklinghausen, are only two manifestations of a congenital defect which, in its widespread involvement, may affect practically any or all of the systems of the body

HEREDITY

The hereditary nature of neurofibromatosis has been conclusively established, but Preiser and Davenport [1] have shown especially well that its inheritance follows regular mendelian principles and that the hereditary factor controlling it is a dominant one They collected 30 cases from the literature in which 2 or more members of a family were affected Uhlmann and Grossman [2] examined 60 members of 3 families with Recklinghausen's disease and found evidence of the disease (either tumor formation or pigmentation) in 13 of these persons In 1 family members of three generations were observed and found to have lesions of striking similarity Stahnke [3] pointed out that the whole disease may be considered a congenital anomaly and that spina bifida, hypospadias, glaucoma and elephantiasis are only a few of the congenital defects commonly associated with neurofibromatosis Thus, it would appear that the cause of the disease usually lies in defective germ plasm

HISTOPATHOLOGIC FEATURES

There has been some difference of opinion as to the cellular origin of the neurofibroma Masson [4] stated the belief that this tumor is

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1 Preiser, S A, and Davenport, C B Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance, with Description of a Case, Am J M Sc **156** 507, 1918

2 Uhlmann, E, and Grossman, A Von Recklinghausen's Neurofibromatosis with Bone Manifestations, Ann Int Med **14** 225, 1940

3 Stahnke, E Ueber Knochenveranderungen bei Neurofibromatose, Deutsche Ztschr f Chir **168** 6, 1922

derived from the sheath of Schwann cells and proposed the term "schwannoma" as a more fitting term than neurofibroma He substantiated his contentions with experimental work on animals Penfield and Young,[5] on the other hand, expressed the belief that the tumor does not arise from nerve tissue but that it is produced from fibroblasts and preserves the peculiar characteristics of connective tissue It is made up of collagen fibers which stain selectively with reticulin stains, in addition to this selectivity in staining reaction, the fibers possess morphologic characteristics which mark them as distinctively connective tissue, rather than nerve tissue, inasmuch as there are no fusiform enlargements or collaterals In addition, when this tumor becomes malignant, it gives rise to sarcoma

If it is true that the neurofibroma arises from mesenchyme, it is not surprising that skeletal defects should commonly accompany the disease Some of the most common and the most remarkable lesions associated with neurofibromatosis are those affecting the skeletal system

OSSEOUS LESIONS ASSOCIATED WITH NEUROFIBROMATOSIS

Brooks and Lehman [6] classified the bony changes of neurofibromatosis under three general headings, as follows (1) scoliosis, (2) abnormalities of growth of individual bones, (3) irregularity of outline of bones, ranging from central or subperiosteal cysts to pedunculated subperiosteal tumors

LESIONS OF THE SKULL

The bones of the skull are commonly involved in this disease Pfeiffer,[7] Rosendahl,[8] Farberov,[9] LeWald,[10] Wheeler,[11] Moore [12] and

4 Masson, P Experimental and Spontaneous Schwannomas, Am J Path **8** 367, 1932

5 (*a*) Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, p 974 (*b*) Penfield, W, and Young, A W The Nature of von Recklinghausen's Disease and the Tumors Associated with It, Arch Neurol & Psychiat **23** 320 (Feb) 1930

6 Brooks, B, and Lehman, E P The Bone Changes in Recklinghausen's Neurofibromatosis, Surg, Gynec & Obst **38** 587, 1924 Lehman, E P Recklinghausen's Neurofibromatosis and the Skeleton, Arch Dermat & Syph **14** 178 (Aug) 1926

7 Pfeiffer, R L Roentgenography of Exophthalmos with Note on Roentgen Ray in Ophthalmology, Am J Ophth **26** 724, 1943

8 Rosendahl, T Some Cranial Changes in von Recklinghausen's Neurofibromatosis, Acta radiol **19** 373, 1938

9 Farberov, B J Rontgenologisches Schadelbild bei Neurofibromatosis Recklinghausen, Ztschr f Augenh **89** 81, 1936

10 LeWald, L T Congenital Absence of the Superior Orbital Wall Associated with Pulsating Exophthalmos Report of Four Cases, Am J Roentgenol **30** 756, 1933

(Footnotes continued on next page)

Uhlmann and Grossman,[2] to mention a few, have reported lesions involving the skull Bulging of circumscribed areas, peculiar vascular designs, enlargement of the sella, enlargement of the orbit and of the optic canal, various types of gross asymmetry, subperiosteal cysts and "bony atrophy and erosions" are some of the most commonly mentioned defects of the skull Bony defects could be due to destruction of bone by neurofibroma, or they could be congenital defects It is probable that maldevelopment of bone does occur and that bone is eroded or atrophied because it is involved with tumor Moore[13] expressed the belief that these lesions of bone are not due to invasion or erosion because these defects are frequently remote from the tumors This fact is well illustrated in the case of neurofibromatosis with defect in the orbital wall, inasmuch as there is no orbital tumor present in some instances

DEFECTS IN THE WALL OF THE ORBIT

Defects in the wall of the orbit, permitting free communication between the intracranial cavity and the orbit, are not often mentioned in the literature, but we have encountered 5 cases in a ten year period which would lead us to believe that the syndrome is not as rare as might be inferred from the paucity of reports concerning it LeWald has shown that unrecognized orbital defects were present in published cases of neurofibromatosis He collected from the literature several cases of pulsating exophthalmos which was not recognized as being due to a defect of the orbital wall, although in reproductions of roentgenograms accompanying the reports it was possible for LeWald to determine that such defects were present It is perhaps significant that only a few observers have published cases of orbital defects, although some of these observers reported several cases of neurofibromatosis, a fact which may indicate that these lesions are recognized, as a rule, only by those already familiar with them

In all 7 cases of neurofibromatosis of the orbit presented by Pfeiffer marked deformities of the bony orbit were revealed roentgenographically In 5 of the 7 cases a deformity of the optic foramen existed, and in 1 case the optic canal was entirely absent In 2 of Pfeiffer's[7] cases extensive defects were present in the orbital walls, permitting direct communication of the orbit with the intracranial cavity Rosendahl[8] reported 8 cases of neurofibromatosis associated with changes in cranial bones In 1 of these cases there was typical roentgeno-

11 Wheeler, J M Pulsation of the Eyeball Associated with Defects in the Wall of the Orbit, Bull Neurol Inst New York **5** 476, 1936

12 Moore, R F Diffuse Neurofibromatosis with Proptosis, Brit J Ophth **15** 272, 1931

13 Moore, B G Some Orthopedic Relationships of Neurofibromatosis, J Bone & Joint Surg **23** 109, 1941

graphic evidence of absence of the roof of the orbit and in another a defect in the lateral wall of the orbit Rockliffe and Parsons [14] reported a case of plexiform neurofibroma of the orbit in which postmortem examination showed that the whole orbital plate of the frontal bone, the lesser and greater wings of the sphenoid bone and the lacrimal plate of the ethmoid bone were missing Farberov [9] reported 3 cases and LeWald [10] 4 cases with definite defects in the walls of the orbit LeWald was the first to point out that this combination of neurofibromatosis and defect in the orbital roof is congenital and is not due to erosion or compression by the growth of the tumor, as other authors had assumed it to be Wheeler [11] reported 5 similar cases (2 of these cases had previously been reported by LeWald), A E Moore [15] reported 2 cases, and R F Moore,[12] van der Hoeve [16] and Avisonis [17] each 1 case, as did Heublein, Pendergrass and Widmann [18]

REPORT OF CASES

Because of the relative rarity with which these cases have been reported and because, as has been mentioned previously, it would appear that this syndrome is usually not recognized when seen, we feel that 5 cases seen at the University of Minnesota Hospitals in the last ten years should be reported In all these instances a typical picture of the syndrome was presented, and perhaps the cases should have been readily recognized, but, as will be seen, some were not recognized immediately because of unfamiliarity with this feature of neurofibromatosis

CASE 1—R N, a 20 month old white boy, was first seen at the University Hospitals Dec 6, 1934 The history of birth revealed nothing unusual At the time of his admission there was a history of protrusion of the eyeballs, most pronounced on the left, which was first noticed three days after birth There was a serous discharge from the left eye At the age of 4 weeks a definite exophthalmos of the left eye had developed

Physical examination revealed that the child was fairly well nourished There was asymmetry of the skull with prominent parietal bosses The left parietal area showed more protuberance than the right and seemed to bulge about 1 cm There was definite exophthalmos on the left, and the left pupil was irregular and somewhat larger than the right The left orbit seemed enlarged on palpation Tension

14 Rockliffe and Parsons, H Plexiform Neuroma of the Orbit, Tr Path Soc London **55**:27, 1904

15 Moore, A E Neurofibromatosis Associated with Proptosis and Defect of the Orbital Wall, Australian & New Zealand J Surg **5** 314, 1936

16 van der Hoeve, J Doyne Memorial Lecture Eye Symptoms in Phakomatosis, Tr Ophth Soc U Kingdom **52** 38, 1932

17 Avisonis, P Zur Frage uber den Zusammenhang der einseitigen Elephantiasis des Oberlides mit Erweiterung der Sella turcica, Ztschr f Augenh **63**· 235, 1927

18 Heublein, G W, Pendergrass, E P, and Widmann, B P Roentgenographic Findings in the Neurocutaneous Syndromes, Radiology **35** 701, 1940

of the globes was equal on the two sides, and there was no pulsation or bruit over the eye There were typical café au lait spots over the buttocks and the abdomen The remainder of the examination revealed no abnormality

Roentgenographic examination showed definite enlargement of the left orbit, and the wing of the left sphenoid bone was elevated Absence of the roof of the orbit was not recognized in the roentgenograms made at this time A review of the roentgenograms shows that the sella was enlarged, but this was not reported at the time of the original examination The results of laboratory tests were all within normal limits It was suggested by a consultant that Recklinghausen's disease with a congenital anomaly was the cause of the child's condition But this diagnosis was apparently not seriously considered by those directly in charge of the patient, for a course of high voltage roentgen therapy was given, on the assump-

Fig 1 (case 1)—Exophthalmos with downward and forward displacement of the eye The left frontotemporal region is protuberant

tion that the underlying condition was a retrobulbar tumor This treatment, of course, resulted in no improvement

The patient was then seen in the outpatient department at frequent intervals for the next several years, on Aug 17, 1939 a neurosurgical consultant again saw the patient and expressed the belief that the underlying disease was probably neurofibroma associated with a defective orbital roof For this reason, a left transfrontal craniotomy was performed by one of the junior staff, who failed to recognize an absence of the orbital roof, instead it was thought that an angioma had been found and that this had produced the exophthalmos by extension into the orbit (fig 1)

Shortly thereafter an encephalogram was made, which showed the tentorium cerebelli to be unusually high, indicating a large cerebellum and posterior fossa There was slight dilatation of the left lateral ventricle At this time deformity of the skull was again demonstrated in the roentgenograms and was reported as a

"large left middle fossa, erosion of the wing of the sphenoid bone on the left and enlargement of the left orbit" (A review of these roentgenograms [fig 2] reveals the typical appearance of absence of the orbital roof, although this was not recognized at the time)

In June 1941 the patient was again admitted to the hospital, with a history of vomiting, headaches, dizziness and weakness, all of which had been present for one year These symptoms had progressed to complete disability and prostration Examination at this time revealed a pulsating, but not expansile, proptosis of the left globe, with neither bruit nor thrill The eyegrounds were normal There was bulging of the skull over the left frontotemporal region, and a violent nystagmus to the left occurred when the head was turned in that direction Evidence of a mild degree of increased intracranial pressure was demonstrated roentgenographically The child improved under conservative management and was discharged from the hospital

In May 1942 the child was again admitted to the hospital, and another exploration of the cranial cavity was undertaken by reopening the former transfrontal craniotomy area, with the idea that a retrobulbar tumor, if present, could be

Fig 2 (case 1) —Enlarged left orbit with absence of its roof, as indicated by absence of the orbital fissures and optic foramen Anchoring wires are placed in the reconstructed roof of the orbit

resected or that absence of the roof of the orbit might be repaired if it were found A plastic reconstruction of the defect in the orbital roof was made with a Lucite plate and a piece of bone taken from the edge of the defect in the skull These were fastened medially to the remnants of a small shelf of the orbital roof, most of it consisting of cribriform plate, and laterally they were anchored to the skull with silver wire Thus, a fairly satisfactory roof was made for at least the anterior portion of the defect in the orbital roof The postoperative course was rather stormy, but the child recovered, and the exophthalmos seemed definitely improved

The child's last admission was on July 25, 1943 The history in the interval was one of gradual improvement for approximately twelve months after the operation, but two months previous to his final admission there developed severe occipital headaches, anorexia, weakness, fatigue and vertigo Examination revealed irregularity of the left pupil with gross nystagmus of the right eye Typical café au lait spots were again noted, not only on the trunk but on all extremities There were no cutaneous nodules There was weakness of the extremities on the right side

The superficial abdominal reflexes were decreased on the right, and the cremasteric reflexes were absent The knee jerk was absent and the ankle jerk diminished on the right side The course of the illness was progressively downhill, and the child died Aug 8, 1943

Postmortem examination of the base of the brain revealed slight enlargement of the left cerebral hemisphere with a slight displacement of the optic system The inferior surface of the cerebellum was covered with a gelatinous tumor, measuring 6 by 5 cm The medulla was enlarged to about twice its normal size, and its posterior surface was incorporated in the gelatinous mass Midsagittal section revealed a large astrocytoma of the medulla, about 4 by 3 cm It partially filled the fourth ventricle and invaded the cerebellum (fig 3) Unfortunately, the defects in the skull were not described in the autopsy protocol

Comment.—Several interesting features are illustrated in this case The exophthalmos was first noticed three days after birth, this in itself

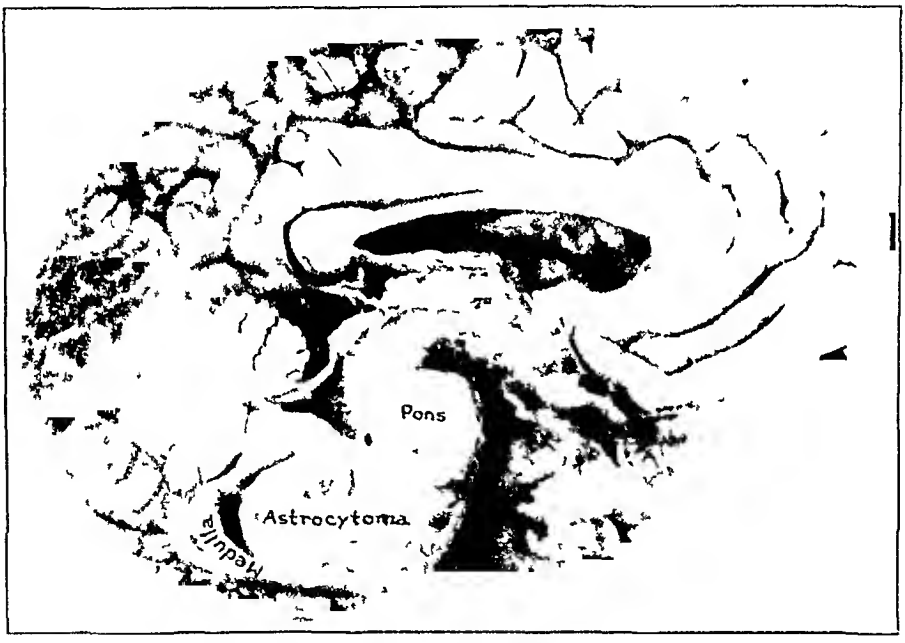

Fig 3 (case 1).—Astrocytoma of the cerebellum

would be a strong indication that some congenital anomaly was causing the condition Temporal or parietal bossing has been reported repeatedly as one of the common changes in the skull associated with neurofibromatosis [19] This was also noted in 4 of the 5 cases we observed, the roentgenograms showing bulging in the temporal region on the side of the tumor

The importance of irregularity of the pupil, as demonstrated here, was emphasized by Davis,[20] who showed that it may be an important

19 Cooper, L Plexiform Neuroma of Upper Lid and Temporal Region, Tr Ophth Soc U Kingdom **26** 136, 1906 Rosendahl [8] Moore [12]

20 Davis, F A Primary Tumors of the Optic Nerve (a Phenomenon of von Recklinghausen's Disease), Arch Ophth **23** 735 (April) 1940

aid in the early diagnosis of the condition, especially if there is involvement of the optic nerve He presented 2 cases with progressive irregularity of the pupil due to neurofibromatosis associated with glioma of the optic nerve In 1 of his cases the signs were minimal, and even post mortem only microscopic infiltration of the optic nerve was found

At the first operation in this, our first, case the presence of a vascular anomaly was reported While this was an erroneous interpretation, such anomalies occasionally accompany neurofibromatosis Rosendahl [8] reported such a case in which an abnormal vascular design in the skull was shown roentgenographically Hydrocephalus is rather commonly associated with neurofibromatosis, although in this case it was probably due to the neoplasm in the posterior fossa Of the 5 cases in this series, roentgenographic evidence of increased intracranial pressure was present in 3, and in the only case in which an encephalographic examination was made hydrocephalus was demonstrated (case 1) The only cases in which no evidence of increased intracranial pressure was shown were those of the 2 adults Zentmayer [21] presented a case of neurofibromatosis with hydrocephalus

Other types of tumors, both of the brain and of the body in general are frequently found in association with neurofibromatosis, as was true in this case As Hosoi [22] pointed out, these growths frequently represent malignant change in one of the neurofibromas, since approximately 13 per cent of neurofibromas undergo malignant change But, in addition to these malignant degenerations, tumors of other types, having no direct relation to the neurofibromas, are commonly seen Davis reported 2 cases of neurofibromatosis, 1 of which was very similar to this case The case was one of a 4 year old child who was operated on for glioma of the optic nerve and who died four years later with an astrocytoma of the temporal lobe on the same side Rosendahl [8] emphasized the frequency with which gliomas and meningiomas are found associated with neurofibromatosis and presented 2 cases associated with oligodendroglioma of the optic nerve

The cafe au lait spots which were present should, of course, have immediately established the diagnosis of neurofibromatosis in this child

Surgical treatment, if it becomes necessary for relief of the exophthalmos, should consist of reconstruction of the roof of the orbit Enucleations have been done either on account of an erroneous diagnosis or for relief of severe exophthalmos In other cases a retrobulbar neurofibroma has been removed by the Kronlein operation In the latter procedure, at least the globe is not sacrificed, and if a large amount

21 Zentmayer, W A Case of Plexiform Neurofibroma Involving the Orbit, Tr Am Ophth Soc **13** 205, 1912

22 Hosoi, K Multiple Neurofibromatosis (von Recklinghausen's Disease), Arch Surg **22** 258 (Feb) 1931

of tumor tissue is present and removed the exophthalmos may be improved But defects in the roof of the orbit which may be contributory to the exophthalmos, or even the entire cause of it, are not affected by this operation Thus, since the exophthalmos is due in large part to encroachment on the intraorbital contents by cerebral herniation, reconstruction of the defect in the orbital roof through a transfrontal craniotomy would appear to be the proper surgical procedure Dandy[23] reported 1 case in which this was done, a portion of the skull from the edge of the craniotomy area being used to repair the defect The result was very satisfactory In addition to reconstruction of the roof, tumors within the orbit can be exposed and removed by this approach We used this method in the present case, with some

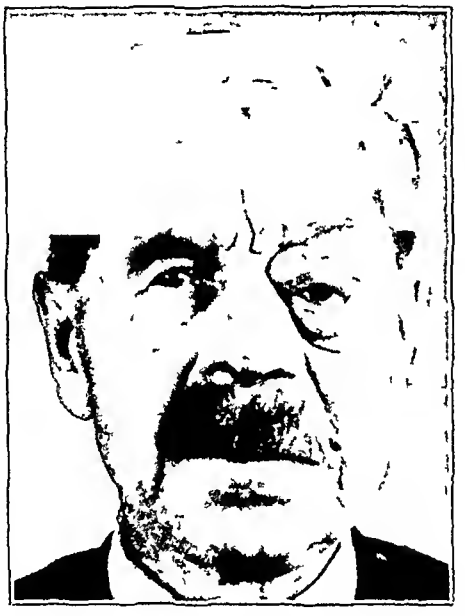

Fig 4 (case 2) —Proptosis of the left eye due to neurofibromatosis The eye is displaced downward and forward

regression in the exophthalmos, but in retrospect it is evident that the cerebral herniation was acting as a decompression in this case because of increased intracranial pressure, which, in turn, was due to a tumor of the cerebellum

Case 2—C K, a white man aged 63, was first seen in the outpatient department of the University Hospitals in March 1936 At this time he gave a history of pain and increased bulging of his left eye for one year He had had mild protrusion and poor vision in this eye since childhood, but he attributed the condition to an injury received early in life However, the exophthalmos had become much worse during the last year

23 Dandy, W E An Operative Treatment for Certain Cases of Meningocele (or Encephalocele) into the Orbit, Arch Ophth 2 123 (Aug) 1929

Examination revealed exophthalmos on the left side, with tenderness on pressure over the left globe and around the left orbital rim The exophthalmometer measurements were 28 mm for the left eye and 18 mm for the right eye (fig 4) The pupil of the involved eye was miotic, reacted to light and in accommodation and dilated with cocaine Fundoscopic examination revealed no abnormalities Visual acuity was reported as follows Distant vision was 20/400 in the right eye and 20/40 in the left eye, near vision was 0 in each eye Near vision in the left eye could be corrected to 14/20 with glasses, but that in the right eye could not be improved with glasses The visual defect in the apparently uninvolved (right) eye was thought to be congenital amblyopia

On the orbital margin of the left malar bone there was a movable firm mass about 1 cm in diameter, which on biopsy was found to be a fibroma directly connected with a nerve There were prominent kyphosis of the lower thoracic and upper lumbar portions of the spine and a bony deformity of the right foot, both

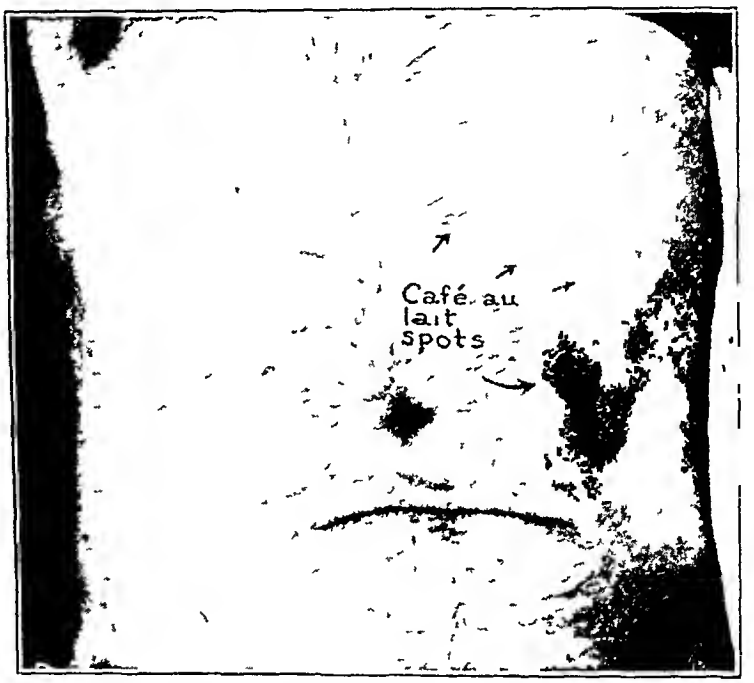

Fig 5 (case 2) —Café au lait spots over the trunk

of which the patient attributed to a fall sustained many years before, but, in reality, they no doubt were lesions of neurofibromatosis There were cafe au lait spots over the trunk (fig 5) The results of laboratory tests, except for roentgenographic examinations, were normal Roentgenographic examination of the skull showed an increase in density of the left orbit, with an increase in diameter of this orbit There was a definite defect in the roof of the orbit, demonstrated by the absence of normal markings The sella was moderately enlarged (fig 6)

In June 1943 a portion of redundant tissue was removed from the left lower lid and on microscopic examination was found to be neurofibroma The roentgenographic changes in the skull were the same as those observed on previous examination

Additional physical abnormalities noted were paralysis of the seventh and twelfth cranial nerves on the right side It was advised that nothing be done at this time because of the extremely poor vision in the right eye However, plastic

repair of the roof of the left orbit was contemplated if the exophthalmos progressed The patient has, however, been observed periodically, and in January 1945 there was still no demonstrable progression

Comment.—The bony abnormalities found in this case were sufficient to indicate the true condition, but the diagnosis was confirmed by biopsy Kyphosis has repeatedly been mentioned as one of the most common bony deformities associated with neurofibromatosis Brooks and Lehman [6] were so impressed with its frequency and importance that they made it the basis of one of the general groups in their

Fig 6 (case 2).—Increased density in the wall of the left orbit Absence of the roof is demonstrated by absence of normal markings within the orbit

classification of these bony changes Deformity of the long bones is also commonly seen

A neurofibroma was found on the orbital margin of the malar bone in this case In most of the cases reviewed a similar neurofibroma was present near the bony deformity, but not necessarily intimately connected with it Thus, in the present case this tumor may be the only one in the area, and a retrobulbar tumor need not be present to produce the exophthalmos Moore [13] showed that this situation holds good but pointed out that there seems to be a segmental relationship between the neurofibroma and the bony deformity He stated the belief that this proves there is a definite etiologic relationship between the two and that it disproves the contention of Brooks and Lehman [6] that the orbital defect is due to invasion of bone by the growth of the tumor

A consideration of possible therapeutic procedures is of interest in this case Because of extremely poor vision in the right eye, an enucleation would leave the patient blind, and a retrobulbar exploration

would probably be fruitless, for there is no evidence that a retrobulbar tumor is present Certainly, the only plausible attack, if it should become necessary to arrest the course of progressive exophthalmos, would be transfrontal craniotomy with reconstruction of the orbital roof

CASE 3—W U, a 7 month old white boy, was first seen at the University Hospitals in September 1936 At this time the parents stated that the child had exophthalmos at birth and that the condition had progressed rather rapidly since

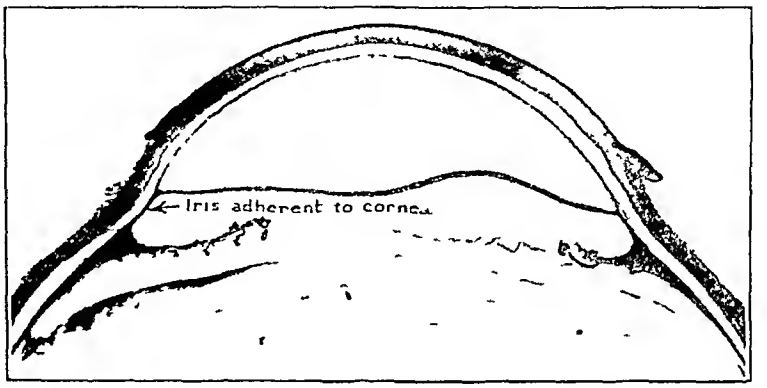

Fig 7 (case 3) —Iris adherent to the cornea, with obliteration of the filtration angle

Fig 8 (case 3) —Protrusion of the left frontotemporal region The right eye has been enucleated for buphthalmos

The history of birth was normal There were two other children in the family, they were in excellent health and apparently had none of the stigmas of neurofibromatosis

Physical examination revealed exophthalmos of the left eye, together with greatly increased intraocular tension, deep anterior chamber, smoky cornea and sluggish reaction of the pupil to light There were two small pigmented areas

on the right flank and a small hemagioma over the left nipple Roentgenographic examination of the skull revealed that the anterior fontanel was somewhat wider than normal for a child of this age The left orbit was larger than the right In November 1936 trephine opening was made in the left globe to relieve the buphthalmos, and this was repeated one month later because of the recurrence of high tension The abnormal tension returned two weeks after the second trephine opening was made

In March 1938 the child was again admitted to the University Hospitals because of rapid increase in exophthalmos during the preceding month This followed a fall, at which time the child hit his left eye

The left eye was enucleated at this time, unfortunately, however, no mention was made of the condition of the orbital wall Examination of the enucleated eye revealed it to be greatly enlarged but otherwise grossly normal Microscopic examination revealed that the iris was adherent to the periphery of the cornea, with obliteration of the filtration angle (fig 7)

In September 1942 the child was again seen, and at this time cafe au lait spots were noted on the abdomen and arms According to the mother, these

Fig 9 (case 3) —Large left orbit with elevation of the roof and absence of the posterior part of the roof

spots had developed since the previous hospitalization Roentgenographic examination of the skull at this time showed a rather large head with widening of the suture lines (fig 8) The sella was enlarged, and the whole appearance of the skull suggested slight hydrocephalus The left orbit was definitely larger than the right, and there was absence of the greater and lesser wings of the sphenoid bone on the left side The roof of the orbit was high and short, and the posterior portion was absent (fig 9) There was also bulging of the temporal bone on the side of the orbital defect

Comment — Congenital glaucoma and buphthalmos have been reported to be associated with neurofibromatosis Anderson [24] collected 33 cases with this association from the literature In 32 of these

24 Anderson, J R Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939, p 166

cases the glaucoma was associated with facial neurofibromatosis and in 1 case with uveal neurofibromatosis only In all these cases the condition was unilateral The author explains the hydrophthalmos on the basis of iris tissue filling the filtration angle In most of these cases the root of the iris is adherent to the periphery of the cornea Microscopic examination of the eye in case 3 showed this to be true In this case there were other characteristic features of neurofibromatosis—pigmentation hydrocephalus and temporal bossing

Case 4—J W, a 16 month old white girl, was first seen in the University Hospitals in July 1944, with protrusion of the left eye and a swollen left cheek,

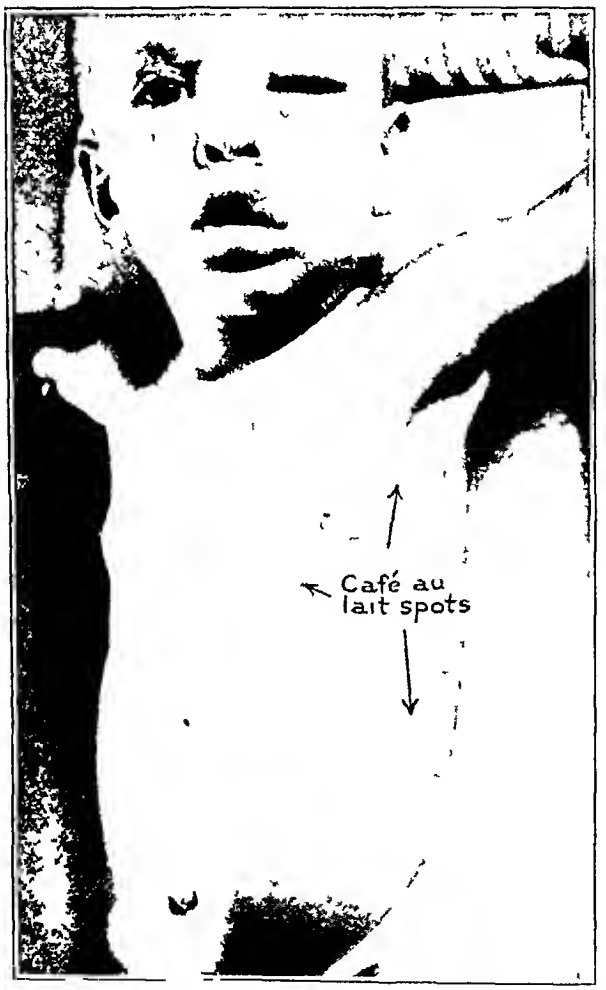

Fig 10 (case 4)—Cafe au lait spots over the trunk, exophthalmos of the left eye, neurofibromatosis about the left eye and over the left side of the face

which was present at birth and had not progressed since that time There was no associated pain, but a serous nasal discharge and a mucopurulent discharge from the left eye were present The child was the first born of a 22 year old mother Pregnancy had been uneventful, and delivery was spontaneous after eight hours of labor

Physical examination revealed that the circumference of the head was 48 cm, with the anterior fontanel open 1 cm and pronounced bossing of the left temporal area There was nonpulsating exophthalmos on the left side, with con-

spicuous edema of the lids and injection of the conjunctiva Auscultation revealed no bruit There were edema of the buccal mucous membrane on the left side and a high arched plate Cafe au lait spots occurred over the trunk (fig 10) Roentgenographic examination demonstrated enlargement of the skull and the left orbit with blurring of detail of the bony wall, although structures corresponding to the greater and lesser wings of the sphenoid bone could be seen (fig 11) There was a definite bulge in the left temporal region, and the sella was somewhat unusual in that there were two depressions one anterior to the other, the anterior depression being in the usual position of the tuberculum sellae The skull was rather large, suggesting the possibility of slight hydrocephalus

Comment.—In this case there were fewer signs pointing to a diagnosis of neurofibromatosis than in any of the other cases in this series Evidence of hydrocephalus was present, as in 2 of the other cases The unusual defect in the sella is an interesting feature There are no reports in the literature of a similar defect associated with neurofibromatosis, but various other sellar abnormalities have been described

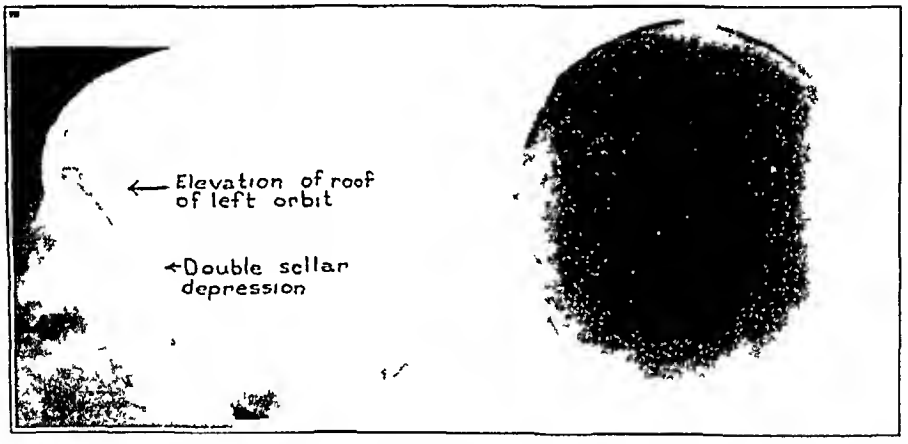

Fig 11 (case 4).—Enlarged left orbit partial absence of the roof of the left orbit and elevation of the remaining portion, double sellar depression

Vogt had 2 cases of neurofibromatosis associated with elephantiasis of the eyelid and enlarged sella and stated the belief that this elephantiasis was due to dysfunction of the pituitary gland Subsequently, LeWald,[10] Farberov,[9] Wheeler [11] and Axisoms [12] have all shown that defects of the sella are rather common with neurofibromatosis and that they do not indicate any disease of the pituitary gland In reviewing the roentgenograms in our 5 cases, it was found that all of them showed an enlarged sella

The only definite evidence of neurofibromatosis in case 4, in addition to the orbital change, was the typical cafe au lait spots It should be emphasized that multiple cutaneous tumors are not necessary to make a diagnosis of neurofibromatosis Penfield and Young [5b] and Preiser and Davenport [1] mentioned that occasionally pigmented spots are the only evidence of the disease throughout life in certain members

of a family while other members may have the more typical tumors To this type of disease picture they have applied the term abortive, or incomplete Rosendahl[8] and LeWald[10] made the diagnosis of neurofibromatosis on the basis of a combination of lesions of bone and typical pigmentary changes Davis[20] made a diagnosis of neurofibromatosis in 5 reported cases without the aid of cutaneous tumors In all the cases there was a tumor of the optic nerve, in 1 there were changes in the bones of the leg, in 1 multiple intracranial tumors, and in all typical café au lait spots In 4 of the cases a positive hereditary history was obtained Davis[20] emphasized the importance of these

Fig 12 (case 5) —Cutaneous neurofibromas, unilateral pulsating exophthalmos

pigmentary changes in making a diagnosis and mentioned that they may be the only positive evidence

Case 5—W S, a 53 year old white man, was seen in consultation in May 1944 but was not admitted to the hospital At that time he complained of pulsating exophthalmos Although this exophthalmos had been present for at least fifteen years, he had never seen a physician about it until February 1944, when he was referred to an internist by an optometrist to whom he had gone for a routine refraction The internist referred the patient to an ophthalmologist, who made the diagnosis of a retrobulbar tumor but had a roentgenographic examination made of the skull This revealed a typical picture of absence of the orbital roof, which was recognized by the roentgenologist as an indication of the presence of neurofibromatosis The patient then came to the neurosurgical service of the University Hospitals for an opinion regarding repair of this defect

The patient had numerous small nodules scattered over his body, these had been present as long as he could remember He wore glasses but stated that he did not believe his vision had become any worse during the last several years There was no family history of neurofibromatosis

Physical examination revealed a well developed, well nourished white man with pulsating exophthalmos on the left side (fig 12) No bruit could be heard The exophthalmos was measured as 24 mm on the right side and 29 mm on the left Visual acuity without correction was 20/50 in the right eye and 20/355 in the left eye, but with lenses it was brought up to 20/20 in each eye The left eye, in addition to its protrusion, was displaced downward The pupils were equal and regular and reacted to light and in accommodation Fundoscopic examination revealed no abnormalities A small tumor was palpable in the lower eyelid It was discrete moderately firm and approximately 7 to 8 mm in diameter Extraocular movements were normal

There was prominence of the temporal area on the left, and a bony defect was palpable just behind the lateral side of the rim of the left orbit This area seemed to be depressed about 1 cm below the level of the surrounding bone

Fig 13 (case 5) —Large left orbit with partial absence of the roof and elevation of the remaining portion

A bony defect was palpable at the angle of the mandible on the left There was no scoliosis, and no other bony abnormalities could be found on physical examination

The skin was covered with numerous small, soft tumors, many of them were pedunculated and a few showed pigmentation, varying from coffee color to deep purple These tumors varied in size from 1 mm to 7 5 cm in diameter Over the left scapula there were two small cafe au lait spots, about 3 cm in diameter

Roentgenographic examination revealed definite enlargement of the left orbit with obliteration of the normal orbital detail (fig 13) There was increased prominence of the left temporal bone, and the sella was enlarged There were cysts in the left malar bone and in the angle of the mandible on the left

Comment.—The patient was scarcely aware of any abnormality in the left eye and certainly was not disturbed by it until the first physician consulted suggested that it might be a serious lesion, even a retinobulbar sarcoma being considered The patient was reassured that it was a benign, and probably nonprogressive, lesion and that no treatment was

necessary When he was last seen, in January 1945, there had been no progression

GENERAL COMMENT

The exophthalmos present in these cases of neurofibromatosis may be due to two factors There may be a retrobulbar neurofibroma or an associated tumor other than neurofibroma, such as glioma of the optic nerve However, the chief reason for the exophthalmos in most of these cases is the encroachment on the orbit by the intracranial contents

In most of these cases a pulsating type of exophthalmos is present These pulsations are due to transmitted pulsations of the cerebrum It should be emphasized that the pulsations are not due to expansion of the orbital content, as with arteriocavernous sinus fistula, and there is no associated bruit, as there is with a fistula Moore [12] operated in 1 such case for arteriovenous fistula before he had recognized this feature of neurofibromatosis Wheeler [11] pointed out that patients who have a portion of the orbital roof removed for exophthalmic goiter (Naffziger operation) may have pulsations of the orbit for a time but these tend to disappear In cases of the Schuller-Christian syndrome there may be similar large orbital defects, but there are no pulsations Wheeler stated the belief that in the case of surgical removal of a portion of the orbital roof this bone is replaced by heavy fibrous tissue, which resists pulsations, and he made postmortem examination in a case of Schuller-Christian syndrome in which the orbital defect was reenforced by a layer of xanthomatous tissue about 3 mm in thickness On the other hand, in Avisonis' case of neurofibromatosis with absence of the orbital roof, in which postmortem examination was made, only a thin membrane separated the brain from the orbit Also, in case 1 of this series, at operation no membrane was found replacing the absent portion of the roof of the orbit Transmission of cerebral pulsations, then, is obviously the reason for the continued pulsations in this condition

SUMMARY

Some of the general features of neurofibromatosis are discussed

A review of the literature reveals that 20 cases of neurofibromatosis with defect in the wall of the orbit have previously been reported

Five cases of neurofibromatosis with defect in the orbital wall are presented, and some of their typical features are discussed

University of Minnesota Medical School (14)

Case Reports

EARLY EFFECTS OF PENICILLIN TREATMENT OF DEMENTIA PARALYTICA

A Clinical and Psychologic Study

LIEUTENANT J EDWARD STERN (MC), U S N R
AND
LIEUTENANT HELEN M CAMPBELL (H) W-V(S), U S N R

The introduction of penicillin has caused a renewed interest in the treatment of early [1] and late [2] syphilis In this paper an account is given of the course of early dementia paralytica in a man aged 31 who at no time was subjected to any other form of therapy Treatment with penicillin appeared to produce a remission Psychologic examinations made before and after treatment confirmed the clinical impression of remission and permitted a roughly quantitative estimate of the degree of improvement Since serologic reversal is often minimal or absent when penicillin alone is used in the treatment of late syphilis, it is suggested that psychologic examinations, repeated at stated intervals, may provide an early indication for repetition of treatment

The clinical methods used in this study were the standard physical neurologic and serologic tests and examination of the cerebrospinal fluid The psychologic methods utilized were the Wechsler-Bellevue Adult Scale [3] for measurement of intelligence and the Rorschach test [4] The Wechsler-Bellevue examination provides a standardized method for determining the intelligence quotient and for revealing disorders of mental functioning The Rorschach test is useful for revealing abnormalities of the personality, chiefly in the area of perception and interpretation of reality

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1 Mahoney, J F , Arnold, R C , and Harris, A Penicillin Treatment of Early Syphilis A Preliminary Report, Ven Dis Inform **24** 355-357 (Dec) 1943 Mahoney, J F , Arnold, R C , Sterner, B I , Harris, A , and Zwally, M R Penicillin Treatment of Early Syphilis, J A M A **126** 63-67 (Sept 9) 1944 Moore, J E , Mahoney, J F , Schwartz, W H , Sternberg, T H , and Wood, W B The Treatment of Early Syphilis with Penicillin, ibid **126** 67-73 (Sept 9) 1944

2 Stokes, J H , Sternberg, T H , Schwartz, W H , Mahoney, J F , Moore, J E , and Wood, W B , Jr The Action of Penicillin in Late Syphilis, J A M A **126** 73-80 (Sept 9) 1944

3 Wechsler, D The Measurement of Adult Intelligence, ed 3, Baltimore Williams & Wilkins Company, 1944

4 Rorschach, H Psychodiagnostik Methodik und Ergebnisse eines wahrnehmungsdiagnostischen Experiments (Deutenlassen von Zufallsformen), ed 4 Bern, Hans Huber, 1941 Klopfer, B , and Kelley, D M The Rorschach Technique, New York, World Book Company, 1942

The patient, a yeoman second class, aged 31, had served in the Navy from 1936 to 1940 and again since Dec 11, 1942, at which time the serologic reaction of his blood (Kahn) was negative A review of the past history indicated that he had had no severe injuries or illnesses He had completed three years of courses in arts and letters in junior college and had gone to work at the age of 23 He had been married for three years During the period of his hospitalization his wife gave birth to their first child, the serologic reactions (Kahn) of both the mother and the child were negative

On Sept 3, 1944, after working in the sun for three hours, the patient felt weak, dazed and confused but did not lose consciousness He was admitted to the hospital on the following day He stated that since February 1944 he had been studying very hard, had been unable to sleep properly, suffered from frequent headache and fatigability, was unable to concentrate and did not feel as if he was "on his toes"

The general physical examination revealed nothing abnormal The neuropsychiatric examination disclosed the following points The pupils were small, but circular and equal and reacted well to light and in accommodation The deep reflexes were symmetrically hyperactive Test phrases were moderately slurred The stream of speech was halting and confused Perception and orientation were only fair Memory was poor and, for recent events, seriously impaired Despite his education his general knowledge was only fair He followed directions poorly

The Kahn and Kolmer reactions of the blood on Sept 10, 1944, were positive (4 plus) Tests of the cerebrospinal fluid made on the same day showed 141 white blood cells per cubic millimeter, of which 99 per cent were lymphocytes, the total protein value was 115 mg per hundred cubic centimeters, the reaction for globulin was positive, and the Kahn and Kolmer reactions were both positive (4 plus) Colloidal gold solution was not available Reexamination of the cerebrospinal fluid on September 20 showed 4 white blood cells per cubic millimeter, the total protein value was 115 mg per one hundred cubic centimeters, the reaction for globulin was positive, the colloidal gold test showed a typical first zone curve, of 5555543200 The urine was normal Roentgenographic examination of the chest showed a normal cardiovascular silhouette and a calcified primary complex in the upper lobe and the hilar region of the left lung The electrocardiogram showed minor variations, including slight notching of the P waves, small Q waves and tall R waves, all in leads II and III, and low voltage of the main deflection in lead IV, but it was considered probably to be within normal limits The records from serial precordial leads were within normal limits

The diagnosis was established as dementia paralytica, although no history of primary or of secondary syphilitic lesions could be elicited, and the serologic reactions of the blood had been reported to be negative as recently as twenty-two months before the patient's hospitalization, or fifteen months before the onset of the first symptoms

On October 3, one month after his entry into the hospital, the patient fell to the ground, had some difficulty in using the right arm and leg but did not lose consciousness Reexamination disclosed no additional abnormalities and there were no sequelae or residual weaknesses

On October 4 penicillin became available, and treatment was instituted, 40,000 units was administered intramuscularly every three hours day and night for a period of eight days, making a total of 64 injections, or 2,560,000 units On October 12 the treatment was completed

On October 6, during the period of treatment, the patient suffered an episode of loss of consciousness of about five minutes' duration There was no convulsion, the eyes were turned upward, the breathing was stertorous, the deep reflexes were hyperactive throughout, there was persistent ankle clonus, and the Babinski reflex and other signs indicative of disease of the pyramidal tracts were elicited on the right There were no sequelae to this attack, and the course of treatment was not interrupted

The serologic reactions of the blood were as follows

Date (1944)	Reaction	Test
October 14	4 plus	Kahn
October 18	4 plus	Kolmer
November 2	3 plus	Kahn
	Positive (40 Kahn units)	Quantitative

On November 4 the Kolmer test gave a 4 plus reaction in four tubes On November 29 examination of the cerebrospinal fluid showed 9 lymphocytes per cubic millimeter, the total protein value was 50 mg per hundred cubic centimeters, the reaction for globulin was negative, the Kahn and Kolmer reactions were 4 plus, the colloidal gold curve was 5555432100 In brief, there were a distinct improvement in the total protein value and a reversal of the reaction for globulin, without change in the serologic reactions or a definite change in the colloidal gold curve

Shortly after the completion of the course of penicillin the patient showed definite clinical improvement Test phrases were well pronounced The stream of speech was free Perception, orientation, memory, both for recent and remote events, and knowledge were definitely improved However clinical examiners found the patient somewhat withdrawn or preoccupied, not quite normally attentive, leaving them with the vague sense of failure to attain full contact or rapport Whether this was an expression of irreversible impairment or part of the preillness personality is not clear

Detailed psychologic studies were carried out before and after treatment With the use of the Wechsler-Bellevue scale, mental examination was made on September 28, before penicillin treatment, and was repeated on October 18 (six days after the last injection), on November 8 (twenty-seven days after the last injection) and on Jan 11, 1945 (ninety-one days after the last injection) The intelligence quotient before treatment was 102, after treatment the ratings were 120, 128 and 131, on the respective dates

On the first examination, before treatment, the following functions were found to be retarded (*a*) memory for acquired facts, with a fund of general information below that of the patient's educational level, and with forgotten facts in some instances covered up by approximations, (*b*) immediate auditory memory span, with a limit of 6 digits forward and 4 digits backward, (*c*) perception of form and structural relations, (*d*) visual-motor coordination, (*e*) ability to do new thinking, (*f*) balanced mental control, with reduction of awareness, autocriticism and judgment

On the second examination, six days after the last injection, there was improvement in every function, with the level of success indicated by an intelligence quotient of 120 The difficulties already mentioned, however, were still clearly in evidence There was some rigidity of mind, in that the patient could not reverse a digit series greater than 4 or improve on answers to questions in verbal reasoning tests, though they were recognized by him as unsatisfactory

Verbal expression was cumbersome, and he had difficulty in thinking of appropriate words

On the third examination, twenty-seven days after the last injection, the intelligence quotient was 128, and on the fourth examination, ninety-one days after the last injection, it was 131 (There was no essential change in mental ability between the third and the fourth examination, the increase of 3 points in the intelligence quotient was clearly attributable to the effect of practice)

As just indicated, while part of these successive increases in the quantitative score was attributable to the effect of practice, qualitative changes were distinct and dramatic Nevertheless, minor qualitative difficulties were still noticeable in fine motor coordination (handwriting), in visual-motor coordination, in memory (as shown by the halting nature of the stream of verbal association and difficulty in recalling the correct word desired) and in impaired flexibility of mind (difficulty in seeing various phases of a problem and in accepting and remembering corrections)

Samples of test responses on the first, second, third and fourth examinations are reproduced

General Information

What is a thermometer?

1 Degrees, Fahrenheit
2 To measure heat and cold
3 To measure temperature
4 An instrument to measure temperature

How far is it from Paris to New York?

1 3,500 miles
2 4,000 miles
3 5,000 miles
4 3,500 miles

Who wrote Hamlet?

1 Longfellow
2 The only one I can think of is Longfellow, but I don't think that is right
3 Shakespeare
4 Longfellow

Who discovered the North Pole?

1 Erickson
2 Peary
3 Peary
4 Peary

What is the capital of Japan?

1 Kobe
2 Tokyo
3 Tokyo
4 Tokyo

What does the heart do?

1 Beats, pulses, pulses the blood
2 Circulates the blood
3 Circulates the blood
4 Circulates the blood

Comprehension

Why should we keep away from bad company?

1 I'd say bad company breeded trouble [Explain further] You would naturally be considered bad company and be treated thus by others
2 It breeds disorder [Explain further] Birds of a feather flock together You are judged by the company you keep This is not the best answer, but it is OK, I guess
3 You are judged by the company you keep It has a bad influence on you
4 We will get in trouble ourselves because we will come to hold the thoughts that breed disorder We are also judged by the company we keep

Why does land in the city cost more than land in the country?

1 Because of improvements made by the city from the taxes of the people
2 Because of constant improvements [Explain further] Taxes are being constantly levied for streets, sidewalks and parks
3 Because of the improvements made through the use of taxes levied on the people
4 Because of the improvements and because it is near the heart of industries

Why are people who are born deaf usually unable to talk?

1 Sound has never crossed their lips That doesn't sound right—sound has never crossed their lips
2 They have never been receptive of speech, so they can't speak it [Explain further] They can't utter a sound That's it They can make noises but can't utter a sound
3 They haven't perceived sound, so can't utter sound Or, they can't imitate because they can't hear
4 They have never been able to perceive sound, so they can't pronounce sound or words

Rorschach records were obtained on September 28, before penicillin treatment, these were repeated on October 19, on November 27 and on Jan 11, 1945. (seven days, forty-six days and ninety-one days, respectively, after the last injection)

The first Rorschach record, obtained before treatment, showed a general expansion of the personality, with reduction in mental control There were excessive spontaneity and imagination, slight resemblances (poor form concepts) were interpreted to a degree greater than normal There was a preponderance of interpretations of movement (of a total of 38 scorable responses, there were 8 interpretations of human figures in motion, 8 of animal figures in motion and 2 of inanimate objects in motion) This should be contrasted

with the occurrence of 3 interpretations using color (secondary to form) in the concept and 3 interpretations using shading for surface texture (secondary to form) in the concept This pattern of response to the Rorschach test is almost the reverse of that obtained by Oppenheimer and Speijer [5] in a case of dementia paralytica The remainder of the interpretations (34 per cent) were pure form concepts, unenlivened by color, shading or movement Poor memory was exhibited, inasmuch as 12 of 50 interpretations originally given were for-

Data on Cerebrospinal Fluid, Serologic Reactions of Blood and Psychologic Examinations in the Course of Penicillin Treatment in a Case of Dementia Paralytica

	Cerebrospinal Fluid						Blood		Psychologic Examination	
Date	Cells per Cu Mm	Total Protein, Mg per 100 Cc	Globulin	Kahn Reaction	Kolmer Reaction	Colloidal Gold Curve	Kahn Reaction	Kolmer Reaction	Intelligence Quotient*	Rorschach Record
1944										
Sept 10	141	115	Positive	4+	4+	Not available	4+	4+		
Sept 20	4	115	Positive			5555543200				
Sept 28									102	Expansion of personality, 50 responses
Oct 4-12	Treatment 2,560,000 units of penicillin intramuscularly									
Oct 14							4+			
Oct 18								4+	120	
Oct 19										Constriction of personality, 19 responses
Nov 2							3+			
Nov 4								4+		
Nov 8									128	
Nov 27										Further constriction of personality, 10 responses
Nov 29	9	50	Negative	4+	4+	5555432100				
Dec 12							4+	4+		
1945										
Jan 11									131	No essential change, 15 responses
Feb 5-12	Treatment 2,400,000 units of penicillin intramuscularly									
March 8	13	40	Negative	4+		5554321000				

* Wechsler Bellevue scale

gotten by the patient on the second, and immediate, exposure of the cards during inquiry There were no interpretations of deteriorated form quality or of bizarre concepts The mood was mildly euphoric

The predominant change from the record obtained before treatment to the subsequent three records, obtained after treatment, was in the direction of increased mental control with notable inhibition and general constriction of the personality There was a reduction in the total number of interpretations from

5 Oppenheimer, E, and Speijer, N Results of Rorschach Test in Case of General Paralysis Before and After Malarial Cure, Psychiat en neurol bl **41** 386-391 (May-June) 1937

50 before treatment to 19, 10 and 15, respectively, on subsequent examinations after treatment The fourth record, unfortunately, was influenced by pressure from the examiner, and the additions to the previous 10 interpretations were only reluctantly admitted by the patient Therefore the examination on November 27, forty-six days after the last injection, is perhaps typical for this patient There was 1 interpretation per card Four of these interpretations were of human figures in motion, and these were of superior conception A reaction to color occurred only on the last card, though its role in the concept was difficult to determine "The nearest I can come is to say this has the characteristic of one of Dali's pictures" The patient revealed himself as having an introverted, meticulous, obsessive-compulsive, mildly neurotic personality structure Irreversible organic mental impairment was not disclosed by the Rorschach test, though a functional disorder, in evidence before treatment with penicillin, appeared to be improved after treatment

In an effort to produce a serologic reversal, the patient was given another course of treatment with penicillin from Feb 5 to 12, 1945 He received 2,400,000 units Examination of the cerebrospinal fluid on March 8 showed 13 white blood cells per cubic millimeter, the total protein value was 40 mg per hundred cubic centimeters, the reaction for globulin was negative, the Kahn reaction was 4 plus, and the colloidal gold curve was 5554321000 As the patient was transferred, further observations could not be carried out

COMMENT

It is recognized that spontaneous remission and intermission may occur in the course of dementia paralytica Nevertheless, it appears likely that the general improvement observed in this case is attributable to the use of penicillin It is further recognized that repetition, familiarity and practice may slightly raise the scores in mental examinations however, it appears likely that the improvement observed was in excess of what might be expected as a result of these factors alone

It would be erroneous to leave the impression that the patient is considered wholly recovered That some irreversible damage has occurred seems likely Though the evidence is subtle, both in clinical and in formal mental examinations the impression is obtained of possible residual mental impairment

It is clear that prolonged observation in cases such as the one reported here is necessary before a reliable evaluation of the results of penicillin therapy of dementia paralytica is to be expected In the light of current data, improvement and reversal of serologic reactions appear to be unusual in cases of dementia paralytica treated with penicillin alone Consequently, it is suggested that psychologic testing at intervals of six months to one year may provide an early indication for the resumption or repetition of treatment, before gross clinical symptoms of relapse make themselves evident

SUMMARY

A case is presented of dementia paralytica occurring in a man aged 31 whose serologic reactions were negative fifteen months before the onset of symptoms

The treatment consisted of two courses of penicillin, no other form of treatment was utilized

Improvement was observed in the general condition, in the cell content, in the total protein and globulin values of the cerebrospinal fluid and in the psychologic scores, while none was found in the serologic reactions of the blood or the cerebrospinal fluid

Subtle evidences of residual mental impairment were persistent

It is suggested that reexamination at stated intervals, with particular reference to psychologic testing, may provide an early indication for the resumption of treatment

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Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Anatomy and Embryology

THE HUMAN PYRAMIDAL TRACT A M LASSEK, J Nerv & Ment Dis 99 22 (Jan) 1944

The belief that the human pyramidal tract is composed of fibers originating in the gigantopyramidal cells of the cerebral cortex has developed as the result of a long series of experiments and observations, culminating in the papers of Grunbaum and Sherrington, of Campbell and of Holmes and May, all appearing in the first decade of the present century After a number of years of study, Lassek concludes that this concept must be questioned in the light of recent anatomic discoveries Because of the relative ease of exciting movements of the contralateral limbs by the electrical stimulation of area 4, the pyramidal tract fibers theoretically should be composed of large myelinated fibers since large cells and fibers are more readily stimulated by electrical currents However, actual fiber counts of the pyramidal tracts reveal that the great majority of the fibers are diminutive (90 per cent being between 1 and 4 microns)

Campbell's reasoning in assigning to the Betz cells the origin of the pyramidal tracts can be criticized as being of a somewhat *post hoc* nature, owing to his acquaintanec with the work of Sherrington and Grunbaum Also, his definition of a Betz cell is faulty, as is his estimate of the number of such cells In addition, there is a distinct disparity between the estimated number of Betz cells and that of the pyramidal tract fibers

The experiments of Holmes and May on retrograde degeneration do not account for the fact that small cells do not exhibit typical changes but, instead often disappear without a trace, so that injury to their axonal fibers would not reveal the fact that the fibers originated from them The relatively small number of Betz cells (25,000 to 34,000) could not possibly account for the large number of pyramidal tract fibers

On the other hand, some investigators, using either a stain for myelin sheaths or a silver technic, have found that many small fibers are left intact in the pyramids after removal of area 4

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THE ANTERIOR CEREBRAL ARTERY IN THE MACAQUE MONKEY (MACACA MULATTA) JAMES B CAMPBELL and FRANCIS M FORSTER J Nerv & Ment Dis 99 229 (March) 1944

In the macaque, the anterior cerebral artery supplies the following structures the optic chiasm, the paleo-olfactorium, the inferomedial part of the head of the caudate–putamen mass and the anterior part of the medial two thirds of the globus pallidus, as well as the inferior aspect of both limbs of the internal capsule, the anterosuperior portion of the thalamus, the corpus callosum, the cortex of the medial surface of the hemisphere as far back as the parieto-occipital fissure and a cortical strip on the lateral surface In a number of macaques, injection studies, using crystalline gelatin dissolved in india ink, were carried out at varying times after ligation of the anterior cerebral arteries When the ligation was carried out at the level of the genu of the corpus callosum, there resulted retardation, underactivity, prehensile difficulty, weakness of the legs and a positive Babinski sign Occlusion at the level of the confluence of the arteries caused postural changes in addition to those already noted, which were more severe Occlusion at the origin of the arteries resulted in coma, followed by stupor and, finally, by underactivity The postural changes, plantar signs and underactivity were all greater than in the

preceding operations Neuropathologic changes included softening of the corpus callosum and infarction of the cortex of the frontal lobe Microscopically, there was noted diffuse involvement of cortical cells extending from the frontal to the occipital lobe, particularly in the former, in addition, there were cellular changes in the head of the caudate nucleus, perivascular demyelination of the internal capsules and occasional glial scars in the ventral thalamic nuclei

The studies indicate that ligation of the anterior cerebral artery is not an innocuous procedure and that the changes are more widespread than would be suspected The psychomotor phenomena are probably attributable to the lesions of the anterior frontal lobe, cingulate gyrus and thalamus, while involvement of the basal ganglia may account for the postural changes, masklike facies and occasional tremulousness However, in view of the widespread lesions, particular symptoms cannot be definitely ascribed to lesions of specific areas

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Physiology and Biochemistry

EMOTIONAL FACIAL EXPRESSIONS OF CATS IN BULBOCAPNINE CATATONIA HERMAN DE JONG and ETHEL CHASE, J Nerv & Ment Dis **98** 478 (Nov) 1943

One of the authors (H de J) has produced experimental catatonia in animals with bulbocapnine (hydrochlorate or phosphate), the state consisting of catalepsy, resistance to change of position and autonomic phenomena, such as polypnea and salivation With large doses of the drug, hyperkinesia and abnormal postures are also produced In addition, the facial and vocal expressions of the intoxicated animals show a series of swiftly changing and characteristic features These changing expressive attitudes were sketched by one of the authors (E C), an artist, under the supervision of the other author Five cats were studied in this manner after the intramuscular injection of 20 to 40 mg of bulbocapnine phosphate per kilogram of body weight Five drawings which typify the gamut of emotional expressions observed in the animals, together with two sketches of patients in catatonic states, are presented These drawings show that definite changes in facial expression occur, including such intense emotional reactions as crying and howling The authors conclude that while it is impossible to judge the nature of pathologic emotional states in animals, the facial and vocal expressions observed and recorded in the cats show evidence of such states, occurring either spontaneously or as an inadequate reaction to external circumstances

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A REACTION AROUND CEREBRAL VASCULAR LESIONS AND ITS BEARING ON CEREBRAL LOCALIZATION LELAND B ALFORD, J Nerv & Ment Dis **99** 172 (Feb) 1944

Alford discusses the discrepancies in attempts at cerebral localization in such conditions as the aphasias and allied syndromes The failure of anticipated effects to develop from lesions of certain areas, as well as the occurrence of improvement in cases in which the supposed source area was presumably destroyed, has been explained by von Monakow on the basis of diaschisis and by the relearning, or "round-about," psychologic solution of Goldstein Others have mentioned the possibility of a shift in cerebral dominance occasioned by forced changes in handedness The usual explanation for phenomena of this type is the assumption of function by other parts of the brain, especially by corresponding areas of the opposite hemisphere Alford believes the most important factor to be the reactions which occur in the cerebral tissues surrounding the foci of actual destruction in vascular softening

In support of this theory, the author cites material from Henschen's collection, in which hemiplegia occurred in a number of cases in which the lesion destroyed only a part of the motor cortex or was far distant from any part of the motor tract A study of 12 cases of homonymous hemianblyopia due to old vascular lesions demonstrated that there was a general involvement of the optic radiation,

a condition that could be produced not by a direct destructive effect but by a widespread, evenly distributed change

The nature of the postulated reaction in the normal tissues beyond the limits of the visible lesion is not clear The author suggests that the cerebral structure has a unique response to injury in the nature of some obscure physicochemical mechanism

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THE CLINICAL AND PHYSIOLOGICAL SIGNIFICANCE OF MAYER'S PHALANGEAL REFLEX L HALPERN, J Nerv & Ment Dis **99** 264 (March) 1944

Absence of Mayer's reflex spontaneous extension and adduction of the thumb produced on maximal passive flexion of the second or third finger at its basal joint has been considered evidence of a lesion of the contralateral pyramidal tract In refutation of this view, Halpern presents a number of cases of cerebellar disease or chorea in which the reflex was absent All the cases were characterized by marked hypotonia of the arm in which the phalangeal reflex was absent without any evidence of disease of the pyramidal tract Thus, absence of the phalangeal reflex does not indicate cortical disease but, instead, occurs only as a result of diminished muscular tone, whether this is due to choreic, cerebellar or pyramidal factors This explanation accounts for the absence of the reflex with paresis of the median or ulnar nerve, injury to the cervical portion of the cord and certain of the myopathies

Contralateral increase in the reflex has occasionally been recorded in cases of tumors of the frontal lobe In cases in which this occurs there are usually also found intensification of Leri's sign and forced grasping The occurrence of these signs in such cases is explained as evidence of increased muscular tone in the affected limb

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A CONTRIBUTION TO THE DIFFERENTIAL DIAGNOSIS OF MYOCLONUS HERMAN DE JONG and LOUIS JACOBS, J Nerv & Ment Dis **99** 290 (March) 1944

Although myoclonus can be readily differentiated from chorea, athetosis, tremor and tic, it is almost impossible to differentiate myoclonus and fibrillation by their external appearance In the case of a 14 year old boy with adventitious muscular movements this diagnostic problem arose and was studied by the authors, who used mechanograms of the muscular activity, recorded with ink-writers on a kymograph Twitchings of the affected muscles were produced during and after muscular activity, during sensory stimulation on any part of the body and as a result of emotion No twitchings were produced by direct stimulation of the muscle or by the intramuscular injection of neostigmine methylsulfate The twitchings stopped completely during sleep All these observations, except the first are indicative of myoclonus and are the opposite of what is found with infiltration Myoclonic movements originate central to the lower motor neuron, while fibrillations probably have their origin in the affected muscle or at the neuromuscular junction

CHODOFF, Langley Field, Va

THE EFFECT OF DESOXYCORTICOSTERONE IN EPILEPSY ROBERT B AIRD, J Nerv & Ment Dis **99** 501 (May) 1944

In keeping with the work which has been done in the study of convulsive states with the use of various agents known to modify the permeability of the cerebral cortex and the blood-brain barrier, Aird employed desoxycorticosterone, which is known to reduce capillary permeability

Groups of white mice were tested for susceptibility to convulsions induced with cocaine hydrochloride after each had received 0 02 cc (0 1 mg) of desoxycorticosterone acetate intraperitoneally It was found that protection against the convulsive effect of the cocaine was afforded only for a short time and was not present twenty-four hours after the administration of the substance

In a group of cats, the convulsive threshold, determined with electrical stimulating and recording technics, was not appreciably altered after the daily administration of 1 mg of desoxycortiosterene acetate intraperitoneally for four days

In 2 patients with clinical epilepsy who had previously failed to respond satisfactorily to the usual anticonvulsant measures, a trial of moderate doses of desoxycorticosterone acetate failed to produce beneficial results

The early protective effect of the substance against cocaine-induced convulsions is probably due to its effect in altering the permeability of the blood-brain barrier This mechanism is similar to that observed in the use of the supravital dyes, vital red and trypan red, except that the effect of these dyes lasts considerably longer The hypothesis of McQuarrie and associates that the anticonvulsant effect of desoxycorticosterone is due to its action in causing electrolytic shifts and corresponding alterations in water balance in the central nervous system is not borne out by the failure of the substance to modify the convulsive threshold as determined by electrical stimulation

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NEUROPATHOLOGICAL STUDIES IN VITAMIN E DEFICIENT RATS RICHARD W HARVEY and JAMES H PERRYMAN, J Nerv & Ment Dis **99** 631 (May) 1944

Harvey and Perryman review the literature on the neuropathologic conditions found in vitamin E-deficient rats Such changes as paralysis, muscular impairment, tremor and loss of righting reflexes have been observed by other investigators in suckling rats born of vitamin E-deficient mothers, and lesions in the central nervous system and muscular degeneration have been demonstrated

A group of 106 rats born of vitamin E-deficient mothers was selected for investigation Half of these received adequate alpha tocopherol and served as controls Extensive neuropathologic studies of the central nervous system involving the use of several staining methods were carried out No significant difference between the control group and the vitamin E-deficient rats was observed The authors suggest that some of the contradictory reports by previous investigators may be due to differences in technic or interpretation

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THE CENTRAL NERVOUS SYSTEM AND HEMATOPOIESIS S P LUCIA and H F MARASSE, J Nerv & Ment Dis **99** 734 (May) 1944

Lucia and Marasse review the literature and undertake a critical analysis of the relation of the central nervous system to hematopoiesis A number of workers have reported the experimental production of reticulocytosis in animals following lesions of the diencephalic-pituitary region, but the significance of this is questionable, since reticulocytosis in the presence of a normal or an elevated erythrocyte count may not be indicative of erythropoiesis The evidence for the existence of an erythropoietic center in the diencephalon or of a hematopoietic hormone in the pituitary gland is far from conclusive A larger amount of experimental evidence in favor of the existence of a leukopoietic center in the central nervous system has been accumulated Rosenow (1928), working with rabbits, concluded that there is a leukopoietic center in the diencephalic area, and Borchardt (1928) confirmed his results There have been a number of reports in which the occurrence of polycythemia, anemia or leukocytosis has been attributed to various pathologic conditions of the central nervous system, such as tumor of the pituitary body or the brain, lesions of the midbrain, narcolepsy, epilepsy, encephalitis, intracranial hemorrhage and cerebral concussion, or has followed lumbar puncture or encephalographic and ventriculographic examination The authors assert that it is impossible to establish a causal relationship between the central nervous system and hematopoiesis on the basis of these reports, many of which are highly theoretic and based on insufficient cases

Fifty-nine cases of disease of the central nervous system with autopsy were studied with relation to the peripheral erythrocyte count and the cellularity of the bone marrow No valid instance of polycythemia was found In no case did qualitative changes in the bone marrow show correlation with lesions of any particular area of the nervous system The authors conclude that any relationship between the lesions and hematopoiesis is fortuitous

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Neuropathology

VARIATIONS OF BLOOD DIASTASE AND GLUCOSE IN DEPRESSION CHARLES S ROBERTS, WILLIAM J TURNER and JAMES H HUDDLESON, J Nerv & Ment Dis **99** 250 (March) 1944

The authors briefly review the literature on the relationship between the psychotic states and the diastase and glucose levels of the blood They emphasize the usefulness of longitudinal studies involving intraindividual comparisons, rather than comparisons of groups of psychotic patients with groups of normal persons Serial determinations on each subject relating changes in the levels on a particular day to changes in the patient's emotional state on the same day are required

A group of depressed patients who were being periodically rated on such items as loudness of voice, speech rate, facial expression of sadness and apathy were subjected coincidentally to determinations of the diastase and glucose contents of the blood It was found that increases in blood glucose were related to increases in loudness of voice, speech rate and increasing sadness as judged from facial expression, while blood diastase activity was related to decrease in loudness of voice and to increase in apathy The authors conclude that a relationship may exist between the glucose level and the diastatic activity of the blood and certain symptoms of depression

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VERTEBRAL FRACTURES IN METRAZOL THERAPY WITH AND WITHOUT THE USE OF CURARE AS A SUPPLEMENT NORMAN L EASTON and JOSEPH SOMMERS, J Nerv & Ment Dis **99** 256 (March) 1944

Eight hundred patients with mental disease given metrazol therapy were studied with reference to spinal injuries Fractures of one or more vertebrae were found in 26 1 per cent of the patients, including 37 2 per cent of the males and 16 8 per cent of the females The incidence of fractures was higher in the age group under 21, owing presumably to the fact that the spine has not yet reached its full adult strength In the 209 patients who sustained fracture, 535 vertebral bodies were involved—581 fractures in males, or 2 8 per patient, and 154 fractures in 73 females, or 2 1 per patient All fractures occurred in the thoracic portion of the spine, involving especially the fourth, fifth and sixth vertebrae In no case did the fracture involve the pedicles, laminas or processes It was found that a preexisting osteoporosis doubled the number of fractures, while kyphosis, scoliosis, arthritis, nuclear change or old fractures did not increase the tendency to injury If fracture did not develop during the first course of metrazol treatment, a vertebral injury was unlikely to occur during subsequent "shock" therapy In patients examined roentgenographically at varying intervals up to two years after the treatment, no delayed or late vertebral changes were found

In a series of 275 patients treated with curare before the induction of the metrazol convulsion, there was a striking decrease in the number of vertebral fractures (from 26 1 to 5 8 per cent) There was also a decrease in the degree of compression and the number of vertebrae involved The authors believe that curare should be used as a supplement whenever metrazol therapy is employed

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Psychiatry and Psychopathology

NEUROPATHOLOGICAL AND PSYCHOPATHOLOGICAL IMPLICATIONS OF BILATERAL PREFRONTAL LOBOTOMY GEORGE W KISKER, J Nerv & Ment Dis **99** 1 (Jan) 1944

Kisker reviews at some length the historical background and development of prefrontal lobotomy and discusses the present views on the procedure from the standpoints of therapeutic implications and experimental psychopathology

Attempts at surgical treatment of insanity date from the trephination rites of primitive man, but it was not until 1936 that Moniz and Lima developed, on a reasoned and scientific basis, a controlled technic for the therapeutic cortical and subcortical intervention This followed a considerable amount of experimentation on functions of the frontal lobe in animals, notably Fulton and Jacobsen's work on primates, and the observations from a number of clinics on the changes in personality and behavior in patients following frontal lobectomy for neoplasm The observations of Ackerly (1935), Brickner (1936) and Rylander (1939) were of special importance Moniz came to believe that certain types of mental disorder were the result of persisting cell complexes of the frontal regions of the brain, and he devised various technics for destroying the tissue, in the belief that a favorable reorganization of behavior would result Moniz' procedures have been refined and extended by both European and American surgeons In this country the pioneer and major work has been done by Freeman and Watts

The operation is concerned primarily with the transection of the neural pathways between the thalamus and the frontal association areas This is done through bilateral trephine openings and the insertion of a cutting instrument, which is swept upward and downward A variety of postoperative pictures are seen, with a prevailing tendency toward either depression or euphoria, depending to a large extent on the preoperative personality organization and to a lesser extent on the plane of the section During the postoperative period a number of transitory phenomena are present Somatic symptoms include bulemia, a positive Babinski sign, vesical and rectal incontinence, vesical retention, ataxia, stupor, aphasia and hemiplegia Emotional symptoms include emotional flattening, diminished spontaneity, lack of attention, loss of judgment, indifference, euphoria, perseveration, talkativeness, disorientation and *Witzelsucht* Freeman and Watts believe that lobotomized patients lose their self-critical power, become more extroverted in behavior and lose their fear of the future Worchel and Lyerly (1941) reported a series of cases in which preoperative and postoperative psychologic examinations were performed They found a lack of intellectual change and a heightened postoperative emotional tone Strecker, Palmer and Grant found postoperatively in a group of 5 schizophrenic patients a disappearance of aggressive tendencies and an increased emotional flexibility but no appreciable intellectual deficiency In a review, covering 500 cases, Drake and Hibbard (1942) conclude that the most suitable patient for lobotomy shows extreme and persistent anxiety and apprehension Specifically, the best results have been attained with anxiety and obsessive-compulsive states, agitated depressions and agitated schizophrenia

The author reports observations on the behavior of 20 psychotic patients subjected to lobotomy Especially striking was the rapidity with which signs of anxiety and tension were relieved and the more or less persistent disorganization of the time schema The profound transformation of the personality patterning was interpreted as a function of affective-emotional restructuralization rather than as an alteration of intellectual processes No measurable impairment in intellectual ability was observed General behavioral changes were similar to those described by other investigators except that the favorable prognostic value imputed by other workers to postoperative dulness and retardation was not found The postoperative confusions so often described were considered to consist more specifically of disturbances in time, space and body schemes

Lobotomy has stimulated interest and curiosity in certain neurodynamic problems of the human brain, namely, the problems of corticothalamic relations, of

autonomic representation in the cortex, of cerebral localization and of somnolence Although the ultimate therapeutic value of lobotomy cannot be assessed, the results are pragmatically encouraging Of the 20 reported cases, there were decided improvement in 35 per cent, slight improvement in 15 per cent and no improvement in 35 per cent The best results were obtained with agitated depressions

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TRAUMATIC PSYCHOSIS A QUESTIONABLE DISEASE ENTITY NATHAN MOROS, J Nerv & Ment Dis **99** 45 (Jan) 1944

Moros discusses the problem of whether it is ever justifiable to make a diagnosis of traumatic psychosis when psychotic behavior occurs in conjunction with headache, dizziness, irritability and fatigability following a head injury Analysis of records from a number of institutions reveal that such a diagnosis is rarely made The author analyzes 41 cases of hospitalized veterans with a condition diagnosed as traumatic psychosis, pointing out in each case that factors other than trauma were of paramount importance in the genesis of the observed symptoms In no case were there sufficient data to justify the tracing of the illness entirely to trauma, although in 25 cases it was thought that trauma played a role in precipitating and aggravating a mental illness basically attributable to other causes The author concludes that the diagnosis of traumatic psychosis as a disease entity is not warranted

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HOMOSEXUALITY A BIOLOGICAL ANOMALY EDWIN G WILLIAMS, J Nerv & Ment Dis **99** 65 (Jan) 1944

Williams differentiates between the male who occasionally indulges in homosexual activity as a substitute for heterosexual relations and the one who habitually prefers to assume the feminine role in homosexual intercourse Men of the latter type are designated as feminine homosexual males During an incidental investigation it was noted that in 2 homosexual males of this type there was no drop in serum cholinesterase activity following the administration of 1 mg of neostigmine methylsulfate, while in sexually normal men such a drop was regularly noted With the manometric method of Rinkel and Pijoan, the serum cholinesterase activity was determined before and after the subcutaneous injection of 1 mg of neostigmine methylsulfate in a group of men of the feminine homosexual type and in 3 control groups, 2 consisting of sexually normal men and 1 of men of the masculine homosexual type With few exceptions, there was a definite reduction in cholinesterase activity in the control groups, while none of the 12 men comprising the group of the feminine homosexual type showed any appreciable decrease The author interprets this observation as indicating a definite biologic difference between the feminine male homosexual group and all others studied

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SIGHING AND OTHER FORMS OF HYPERVENTILATION SIMULATING ORGANIC DISEASE. PAUL A GLIEBE and ALFRED AUERBACK, J Nerv & Ment Dis **99** 601 (May) 1944

It has been shown that deep breathing produces dizziness, numbness and tingling of the extremities and may simulate common diseases, such as heart disease, asthma, peptic ulcer, thyrotoxicosis and convulsive disorders The hyperventilation syndrome usually occurs in the absence of organic disease and is an important mechanism of psychosomatic disease whereby emotional disturbances can produce physiologic and biochemical changes and physical symptoms In susceptible

subjects the authors have observed the appearance of headache, light headedness, dizziness, faintness, breathlessness, palpitation, numbness and tingling of the face and extremities, weakness, confusion and anxiety in a period varying from a few seconds to twenty minutes The biochemical basis for the symptoms is the production of alkalosis due to the increased loss of exhaled carbon dioxide

In testing for symptoms of hyperventilation, the patient breathes in and out deeply until symptoms appear If none are present at the end of three minutes, the test is discontinued provided that it has been observed that the ventilation was tripled or quadrupled If the symptoms produced are those of which the patient originally complained, the relationship should be explained to him

In 4 illustrative cases from a large series, the hyperventilation syndrome was shown to be responsible for symptoms which had previously been diagnosed, respectively, as coronary disease, petit mal, epilepsy and neuralgia In each of the cases the demonstration of the relationship between overbreathing and the patient's complaints served as an introduction to successful psychotherapy In addition, the patients were taught to correct improper respiratory habits

In most of the cases studied there were found such factors as a family history of neurotic tendencies, childhood inadequacy, feelings of frustration or poor marital and sexual adjustments It was frequently found that if sexual relations were unsatisfactory, both husband and wife would show symptoms of hyperventilation The condition was found in women three or four times as frequently as in men, and the age group from 20 to 40 was most frequently represented

In the treatment of the hyperventilation syndrome, psychotherapy is the main weapon Drug therapy, such as phenobarbital and ammonium chloride in 7 5 grain (4 8 Gm) doses (for the acidifying effect) is a relatively unimportant adjunct

The authors believe that the effort syndrome and neurocirculatory asthenia are expressions of hyperventilation

CHODOFF, Langley Field, Va

Diseases of the Brain

THE NEUROLOGIC COMPLICATIONS OF HEMOPHILIA P M AGGELER and S P LUCIA, J Nerv & Ment Dis **99** 47 (May) 1944

The essential defect in coagulation characteristic of hemophilia is a delay in the conversion of prothrombin to thrombin, apparently due to a deficiency of thromboplastin or a thromboplastin-like substance in the plasma Whether the defect is inherent in the plasma or in the platelets is not clear

Lesions of the nervous system are not frequent in cases of hemophilia Aggeler and Lucia, in a review of all known instances of neurologic complications of the disease, were able to find only 45 such cases Three authentic and several somewhat doubtful cases of hemorrhage into the cerebral hemispheres were found No instance of hemorrhage into the cerebral ventricles, cerebellum or medulla and only a single case of hemorrhage into the pons was encountered Hematomyelia as a complication of hemophilia has been reported in 5 cases Primary subdural and subarachnoid hemorrhage has been reported in several cases verified at autopsy One probable case of spinal epidural hemorrhage occurring in association with hemophilia has been recorded, while there have been several cases of spinal subdural and subarachnoid hemorrhage Involvement of the facial, sciatic, femoral, peroneal, median and ulnar nerves has been noted by various observers

The authors give the histories of 3 new cases in which neurologic complications of hemophilia occurred In the first case spontaneous cerebral hemorrhage, as well as chronic arachnoiditis resulting from previous subdural and subarachnoid hemorrhages, was found In the second case there was paralysis of the left femoral nerve, and in the third case, paralysis of the left femoral nerve, in addition to massive hemophiliac pseudotumor of the left ilium

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PAPILLEDEMA (CHOKED DISC) AND PAPILLITIS (OPTIC NEURITIS) THEIR DIFFERENTIAL DIAGNOSIS FREDERICK C CORDES and SAMUEL D AIKEN, J Nerv & Ment Dis **99** 576 (May) 1944

Papilledema is due to disturbance in the normal pressure relationship of the circulation on the two sides of the lamina cribrosa and may be due to ocular, orbital, intracranial or systemic causes Sudden lowering of the intraocular pressure, as well as increased intracranial pressure, may produce the picture Brain tumor is the most frequent single cause and was found to be associated with papilledema in 80 per cent of Paton's series of 252 cases The early appearance of papilledema is characterized by a swelling of the nerve fiber sheaths in a limited area of the disk, followed by elevation of the vessels of the disk and absence of the venous pulse Later, the disk tissue becomes opaque, the margins become obliterated, and the typical elevation of the disk appears Because of the edema, the disk appears to be twice its normal size Arteries are contracted and veins dilated Exudates and hemorrhagic spots usually appear After papilledema has existed for a long time, atrophy sets in, although fully developed choking of the disk can recede without leaving visible evidence Central vision remains normal for a long time There are enlargement of the blindspot and various forms of perimetric defect Pathologically, there is edematous swelling of the nerve fibers, with a rather abrupt termination of the area of edema at the point where the retinal vessels leave the nerve There are important changes in the nerve fibers, ending in degeneration of neural elements

The term "optic neuritis" designates an inflammation of the optic nerve with some signs of involvement of the disk The most important symptom is loss of central vision This is usually accompanied with pain in and behind the eye especially on movement, lowering of dark adaptation and slow dilatation of the pupil after the initial contraction when light is thrown on it The tendency toward recovery is strong Ophthalmoscopically, the disk is hyperemic, owing to dilatation of the capillaries, and there may be an accompanying neuroretinitis The inflammation is usually unilateral, and the swelling is rarely over 2 D Perimetric examination reveals a central scotoma and peripheral contraction Pathologically, there are proliferative changes in the interstitial tissues, primarily perivascular, followed by degeneration of nerve elements with resultant gliosis

The following points are helpful in the differential diagnosis of the two conditions (1) Sudden loss of central vision is the most important sign of papillitis (2) in papillitis the scotoma is central, while in papilledema the central field is preserved until late, (3) there may be cloudiness of the posterior part of the vitreous in papillitis, (4) swelling of the disk venous engorgement and hemorrhages are less pronounced in papillitis, (5) papillitis is usually unilateral and papilledema bilateral, and (6) pain on pressure or movement of the eyeball is characteristic of inflammation of the optic nerve

CHODOFF, Langley Field, Va

THE BRUNS SYNDROME BERNARD J ALPERS and H E YASKIN, J Nerv & Ment Dis **100** 115 (Aug) 1944

Alpers and Yaskin report 5 cases, in each of which the Bruns syndrome was prominent and of great localizing value In 2 of these cases there was a midline medulloblastoma of the vermis, in 2 cases astrocytoma of the cerebellar hemisphere and in 1 case disseminated sclerosis with probable involvement of the vermis by a plaque

The Bruns syndrome is characterized by the development of attacks of vertigo, headache and vomiting on change of posture of the head, by freedom from symptoms between attacks and often by constant anterior flexion of the head, usually in the midline but at times with lateral flexion and rotation Additional, more variable, symptoms, such as amaurosis, teichopsia, tachycardia, respiratory irregularity and syncope may occur The change in posture which produces the

symptoms may be brought about by a change of position of the head in relation to the body, by arising from a reclining to an upright posture, by turning from one side to another, by rotation of the head, by lying down or, indeed, by any change in position of the body in space Passive movement of the head may be of diagnostic aid In the vast majority of cases the Bruns syndrome indicates a lesion in the fourth ventricle or adjacent structures The lesion is usually a tumor, but cysticercosus of the fourth ventricle or multiple sclerosis can cause the syndrome, and it has been reported with tumors of the third and lateral ventricles

The pathogenesis of the symptoms is not clear, although it has been attributed to periodic blocking of the ventricular system on change of posture of the head The authors suggest that irritation of the vestibular nuclei or pathways may be the mechanism responsible for the symptoms

CHODOFF, Langley Field, Va

CEREBELLAR TYPE OF ATAXIA ASSOCIATED WITH CEREBRAL SIGNS ALEX J ARIEFF and LEO A KAPLAN, J Nerv & Ment Dis **100** 135 (Aug) 1944

Arieff and Kaplan report 5 cases, in all of which there were displayed signs and symptoms of dysarthria, cerebellar ataxia, intention tremor, involvement of the pyramidal tract and, at times, dementia and convulsions In 2 of the cases the condition was thought to be due to alcoholism, in 1 case the diagnosis of multiple sclerosis was considered, and the other 2 could not be adequately classified A history of familial or hereditary tendency to the disease was absent in all the cases

CHODOFF, Langley Field, Va

SLEEP PARALYSIS PAUL CHODOFF, J Nerv & Ment Dis **100** 278 (Sept) 1944

Sleep paralysis is defined as consisting of brief periods of complete immobility and powerlessness occurring as a person is falling asleep or as he is awakening The syndrome may be precipitated by terrifying dreams and may be accompanied with hypnagogic illusions The characteristic features of the condition were seen in 2 patients, both of whom presented other manifestations of a narcoleptic nature The similarity between sleep paralysis and cataplexy is probably more apparent than real The author concludes that sleep paralysis is a nondiagnostic symptom which may occur in narcoleptic patients or independently in otherwise healthy persons and that it may be due to a variety of factors

CHODOFF, Langley Field, Va

Treatment, Neurosurgery

RECONSTRUCTIVE ORTHOPEDIC SURGERY FOR DISABILITIES ARISING FROM IRREPARABLE INJURIES TO THE RADIAL NERVE LEROY C ABBOT, J Nerv & Ment Dis **99** 466 (May) 1944

Abbot describes the reconstructive operative procedures used by him in cases of irreparable damage to the radial nerve The first of these is tendon transplantation to correct the wrist drop with inability to extend the fingers and thumb The muscles utilized are the pronator teres, which is transferred from its insertion at the lateral border of the midshaft of the radius to the common radial extensors of the wrist, and the flexor carpi radialis and flexor carpi ulnaris, which are transplanted to the paralyzed extensor muscles of the fingers and thumb The palmaris longus muscle may also be employed The technic used is a modification of that devised by McMurray After operation, the limb is held in a position of dorsal flexion of the wrist with fingers and thumb extended for a period of two weeks, during which time active contraction of the transplanted tendons is begun The results of this operation are often very good In certain cases the ability to dorsiflex the wrist remains weak and the hand grasp ineffective In such cases arthrodesis of the wrist is employed as a supplementary procedure This does not

interfere with rotation of the forearm and is attended with little incapacity, provided motion at the carpometacarpal joints has been preserved

CHODOFF, Langley Field, Va

INTRASPINAL THIAMINE CHLORIDE IN THE TREATMENT OF GASTRIC CRISIS OR LIGHTNING PAINS IN TABES DORSALIS BENJAMIN H KESERT and MAURICE O GROSSMAN, J Nerv & Ment Dis **101** 372 (April) 1945

Kesert and Grossman report the results of treatment of 8 patients with tabetic pains and gastric crises by means of intraspinal injections of thiamine hydrochloride Injections were given up to three or four times a year in doses of 50 to 100 mg After injection the pains were intensified for about twelve hours, but in all cases there was noticeable relief from pain for several weeks or months No harmful effects of any kind were encountered

CHODOFF, Langley Field, Va

MALARIA IN NEUROSYPHILIS J ERNEST NICOLE, J Ment Sc **89** 381 (July-Oct) 1943

Nicole reports on the treatment of 401 patients who were successfully inoculated with malaria by the intramuscular route for neurosyphilis He found that malaria therapy alone gave a good recovery rate but that the addition of drugs gave even better results and that, while tryparsamide may be the drug of choice, other drugs help a great deal Such combined drug and malarial treatment apparently fulfils the function that can be expected of it in at least 50 per cent of cases Even patients with acute or advanced neurosyphilis can make a good recovery

If the first attack of malaria does not produce a cure, a second or a third inoculation may be expected to do so "Cure" in a serologic sense will be more frequent if the Wassermann rather than the more sensitive Kahn test is used The Kahn reaction and the colloidal gold curve are the last to show improvement, whereas the protein content and the cell count are the first and the Wassermann reaction is in between

MCCARTER, Boston

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

PAUL I YAKOVLEV, M D , *Presiding*

Regular Meeting, Dec 21, 1944

Pituitary Tumors and Their Treatment DR OSKAR HIRSCH

From the standpoint of pathologic anatomy, tumors of the pituitary gland and its surroundings are adenoma, craniopharyngioma, meningioma, chordoma, glioma, aneurysm, osteoma, chondroma, cholesteatoma and sarcoma, as well as syphilis, tuberculosis, actinomycosis, xanthomatosis, arachnoiditis cystica and hydrocephalus The last-named processes are not tumors, but they act as such, deforming or destroying the sella The anterior lobe only is the site of primary tumors, whereas the posterior lobe is the place of predilection of metastatic tumors

Microscopically, adenomas of the pituitary gland, constituting about 90 per cent of all tumors, are benign They do not infiltrate the neighboring organs except in a few cases, metastasis being extremely rare Clinically, however, the adenomas have unlimited growth They compress the chiasm and push the neighboring organs aside They destroy the anterior lobe Therefore the patients show loss of sexual function Nearly all the chromophobic and 50 per cent of the eosinophilic adenomas are clinically malignant Owing to the small size of the benign eosinophilic pituitary adenomas, the anterior lobe usually remains intact, and therefore the functions of the sexual organs are maintained

From the surgical standpoint, all tumors of the pituitary region can be divided into four groups 1 Suprasellar tumors, growths situated above the pituitary gland, which may remain normal The sella is usually normal The symptoms are choked disks and irregular visual fields These tumors are approachable only by the frontal route 2 Intrasellar tumors, growths limited to within the sphenoid cavity The clinical symptoms are usually acromegaly, absence of visual disturbances and ballooning of the sella These tumors are easily approachable by the endonasal route 3 Craniosellar tumors, one part of the growth extending toward the brain and the other toward the sphenoid cavity These tumors are approachable by both the frontal and the endonasal route The clinical symptoms are bitemporal hemianopsia, atrophy of the optic disk and loss of sexual function 4 Cystic tumors, growths which consist of, or contain, a cyst Calcification is frequently visible in the roentgenogram These tumors are easily approachable by the endonasal route

I employ my endonasal method, with local anesthesia By means of submucous resection of the septum, the anterior wall of the sphenoid cavity is removed, and the enlarged sella is exposed and opened The tumor is removed by curettement and suction

I have operated on 277 patients with this method in nineteen years The mortality rate was 5 4 per cent, most of the deaths being due to meningitis, which nowadays can be prevented by use of the sulfonamide drugs and penicillin Fifty-six patients (20 per cent) died of recurrences during the nineteen years, 194 (70 per cent) were alive at the end of the nineteenth year

As it is impossible with any method, whether the transfrontal or the endonasal route, to remove a large tumor completely, I use radium to destroy the rest of the growth Neurosurgeons use roentgen irradiation

Exclusive roentgenologic treatment presupposes a solid tumor This therapy is without any effect on cystic tumors but 17 per cent of all tumors of the pituitary region are cystic According to Dyke and Hare roentgen therapy produced

improvement in 26 per cent of patients with chromophobic tumors (47 per cent became worse) and in 40 per cent of the patients with eosinophilic tumors (24 per cent became worse) There are some instances of occurrence of cataract two to seven years after irradiation

Advantages and Disadvantages of the Transfrontal and the Endonasal (Transphenoidal) Method—The statistics for the Cushing series, as reported by Henderson, and for my series are tabulated here

Series		Mortality
Cushing	227 transphenoidal operations	5 3
	101 transfrontal operations	4 5
Hirsch	277 endonasal operations	5 4

The transfrontal method is the procedure of choice for all suprasellar tumors without widening of the sella To all other tumors the endonasal method is applicable

The treatment of cystic tumors is much easier with the endonasal method, and the reopening of the cyst by this route is also an easy procedure

With either method, with the endonasal (transphenoidal) or with the transfrontal, an intracranial tumor cannot be removed entirely To prevent the further growth of the remaining tumor tissue, the neurosurgeon uses postoperative roentgen therapy I apply radium locally My results have been as follows 1 Of patients who had the endonasal operation plus radium irradiation, 76 per cent remained free from recurrences over four years 2 Of patients who had the transfrontal operation plus roentgen irradiation, 87 per cent remained free from recurrence until the end of the fifth year

Henderson's figures, based on Cushing's material, show 57 per cent of patients alive two to twenty years after operation, my figures show 70 per cent

With the transfrontal method, postoperative clotting in the operative field, especially with cystic tumors, appears in 14 per cent of cases This clotting produces pressure on the optic nerves and, according to Henderson, is the most serious objection to this method

The transfrontal method gives poor results in cases of homonymous hemianopsia and central scotoma, which constitute, respectively, 7 and 11 per cent of cases of pituitary adenoma

With the transfrontal method one meets difficulties in the case of a prefixed chiasm In these circumstances the exposure of the tumor requires transection of the chiasm Prefixed chiasm is present in 5 per cent of cases of tumor in this region

With the transfrontal method one risks the development of transient or permanent mental symptoms in elderly people with shrunken convolutions and a dura strongly adherent to the bone (Cairns)

The endonasal method is performed without any external scar and can be done with local anesthesia

The objection to the endonasal method is a spongy sphenoid bone (rare with pituitary tumors)

Both the transfrontal and the endonasal method carry a postoperative risk, namely, clotting with the transfrontal method and meningitis with the endonasal method Since meningitis can be checked by chemotherapy, the endonasal method should be considered in all cases of pituitary tumor in which surgical treatment is indicated

DISCUSSION

DR GILBERT HORRAX I should like to pay my respects to Dr Hirsch It is recognized that he is one of the pioneers in the attack on pituitary tumors, and his endonasal method, or modifications of it, are used by many neurosurgeons in operating on adenomas of the pituitary gland I must apologize for not having statistics on the subject, but I should like to discuss this paper from several aspects

First, as neurosurgeons we see essentially three types of pituitary tumors chromophobic adenoma, eosinophilic adenoma, which produces acromegaly, and the

rare basophilic adenoma I have operated on only 1 adenoma of the last type Patients with chromophobic adenoma usually come to the surgeon or the neurologist because of trouble with vision If the patient is a woman, she may have had amenorrhea for a long time, and some patients have other glandular symptoms The acromegalic patients are concerned chiefly with the changes in their features I am leaving out of consideration all other types of tumors in the pituitary region, as time does not serve to discuss them

It is difficult to decide whether one should operate or try roentgen therapy The transfrontal or the endonasal operation served a great purpose in the early days of attack on these tumors Whether operation is still of value in certain cases I am not sure Very likely there are selected cases in which it should be used Having seen Cushing use the transsphenoidal approach and later abandon it for the intracranial operation, and in view of the better exposure which is possible with the latter, I feel one can almost always accomplish more with this method There are certain cases in which a prefixed chiasm gives little room, but in my experience one gets a much better exposure by working from above A rhinolaryngologist like Dr Hirsch, working perhaps with a special light and other adjuncts, can do a great deal in some cases

The important thing in Dr Hirsch's statistics is the number of recurrences and the number of patients who died of recurrence in the first few years after operation As far as the immediate mortality rate is concerned, there is little to choose between the transfrontal and the transphenoidal operation, but the problem lies in obtaining a radical extirpation of the tumor It seems to me that a much better cleaning out of the tumor is possible by the intracranial route In a case of cystic tumor, the cyst will refill if any remnant of the wall is left behind It is important to remove all of the wall One must strive for as complete an evacuation of the tumor as possible and take out the capsule above the sella Leaving aside all technicalities of the approach, there may be a few selected cases in which the tumor has grown downward and one can get at it better through the nose But most neurosurgeons now are not very familiar with the endonasal route It is rare that one has to operate for acromegaly It is indicated only in the incipient stage, in younger patients with early facial changes I think acromegalic patients do better with roentgen irradiation It also helps their headache

It is difficult to decide when one should operate on an adenoma One has to be guided by the individual case There is a mortality for any operation In cases of the ordinary chromophobic type the mortality should be less than 5 per cent In cases of "malignant" extensive adenoma there is a high mortality rate, but therapy is not of much value anyway For the patients who have moderate visual disturbance and can still earn their living I suggest roentgen irradiation first I always give them the benefit of a trial of roentgen therapy under careful supervision It is my impression that probably about 25 per cent of such patients get sufficient help from roentgen therapy, hence, a trial of this method is warranted Some patients get great visual relief from it, and some get relief from headache When patients who are receiving roentgen irradiation continue to have visual acuity of 20/40 to 20/50 or less, the result cannot be considered good, and such a patient almost certainly should be operated on On the other hand, one has to remember that even though roentgen therapy may carry a patient along fairly well for many years, the tumor may nevertheless be spreading and the time will come when neither irradiation nor operation will help All in all, I do not feel very happy about the results of roentgen treatment of pituitary tumor except in patients who respond promptly and well The surgeon has to decide in the individual case, but the problem is an interesting one and more is being learned about it My own feeling is that I know much more about the intracranial than the transphenoidal route, and I should prefer to attack all pituitary tumors in this way The figures Dr Hirsch gave for Dr Cushing's series were for his early work It is extremely rare to have a postoperative clot now

Dr James L Poppen I enjoyed the paper very much It is rather preposterous of me to say anything on this subject Whereas Dr Hirsch has an

experience of thirty years, with twenty years of postoperative observations, I have only twelve years I have nothing to add to Dr Horrax' discussion except to elaborate on the dangers of roentgen irradiation I feel that this treatment is of value in very early stages I had a patient in the last six weeks who began roentgen treatment two years ago His vision was on the borderline at that time He did not want to be operated on then Therefore I temporized with him and gave him roentgen radiation After the first treatment his vision improved slightly; and his headaches improved He was pleased with the result Six months later his vision became poorer and his headaches were worse A week later scintillating scotomas developed This symptom persisted four or five days and then disappeared, and his headaches improved Six weeks ago he had another series of treatments, again resulting in scintillating scotomas and blindness An emergency operation was performed, and a large hemorrhage into the adenoma was evacuated

More recently I have had a patient who received roentgen treatment, his condition grew worse, and he died before operation could take place One must keep in mind that roentgen therapy has also a definite mortality rate The visual fields should be watched carefully during treatment

Capt James C White (MC), U S N R A case which my associates and I had recently in the Naval hospital illustrates one of the complications for which one could not do much by the intranasal approach to the pituitary The man had had bitemporal hemianopsia with increasing visual disturbance since 1938, together with evidence of hypopituitarism Distinct personality changes had recently developed, and a series of generalized epileptic fits followed The cause of these symptoms was an adenoma of the pituitary gland, which had grown out of the sella turcica and extended forward to the crista galli and caudally to the middle portion of the pons It weighed 150 Gm Jefferson, who has given the clearest account of such unusual parasellar extensions of pituitary adenomas (*Proc Royal Soc Med* **33** 433-458, 1940), reported that they occur in approximately 14 per cent of cases of pituitary tumors, particularly of the chromophobic type Since the tumor may grow upward into the hypothalamus, forward between the frontal lobes, backward beneath the tentorium and, most commonly, laterally into the temporal lobe or the cavernous sinus, such extension may often be missed clinically and can then only be found at the time of the operation if the approach is made by the frontal intracranial exposure In such circumstances little, if anything, could be accomplished by the endonasal route

Dr Oskar Hirsch Most neurosurgeons will not use the endonasal operation because they are not familiar with this method, as I am not familiar with the neurosurgeon's method The point I wish to make clear is that, according to the figures on recurrence and mortality which I presented, the two methods are equally successful There is no reason to neglect a method which has been employed in the greatest number of pituitary tumors If operation is indicated in a case of pituitary tumor, both methods must be considered

Neurocirculatory Asthenia, Effort Syndrome and Anxiety Neurosis Dr Stanley Cobb, Dr Paul D White, Dr Mandel E Cohen, Dr Daniel W Badal, Dr William P Chapman and Dr Robert E Johnson

The clinical picture of neurocirculatory asthenia consists of a large number of symptoms, which occur frequently These include not only cardiovascular-respiratory disturbances but symptoms commonly seen with neuropsychiatric disease Failure to recognize the broad nature of the symptoms has led to much confusion in the literature

The disorder consists of two types, the chronic and the acute Our studies have dealt primarily with the chronic type, represented by patients who were unable to do hard work and who had been emotionally unstable as long as they could remember The chronic type of neurocirculatory asthenia shows a strong familial tendency Studies of normal control soldiers and sick soldiers with osteomyelitis do not reveal this tendency

Work tests (treadmill and step) have been used to determine the amount of hard work that can be expected from the patients Patients do poorly on these tests as compared with normal control subjects The lactic acid response after moderate exercise (treadmill walk) gives a mean of 43 6 mg per hundred cubic centimeters for the patients and a mean of 21 6 mg per hundred cubic centimeters for the normal controls Studies of respiration and response to exercise show that the minute respiratory volume is greater in the patients than in normal control subjects, as illustrated by the Harrison ventilation index, which demonstrates that there is an objective correlate of the patient's subjective feeling of dyspnea The response of the pulse to exercise shows a higher rate and a slower return to normal Studies of the capillaries of the finger nail bed show that the patients have fewer hairpin forms and more looped and unusual forms than do the normal control subjects The incidence of hairpin forms in normal, healthy soldiers is 79 per cent, in soldiers convalescing from wounds complicated by osteomyelitis, 65 per cent, and in patients with neurocirculatory asthenia, 42 per cent

Studies of reactivity to pain, ability to maintain a sustained grip and willingness to stand unpleasant electric shock all yield low values for patients with this disorder This suggests that the patient's disability is not limited to the cardiovascular apparatus alone

Psychologic tests give scores placing the patients in the group labeled "neurotic"

The evidence suggests that the chronic type of neurocirculatory asthenia is a disorder which runs in families, symptoms extend over years of the patient's life, and exacerbations may be provoked by hard work, acute emotion-provoking experiences, chronically emotion-disturbing situations, infection and perhaps other factors

DISCUSSION

LIEUT COMDR HERBERT I HARRIS (MC), U S N R It is a privilege to be invited to discuss this paper by Dr Cobb and his associates, and I am much impressed with the varied points of departure from which this problem has been approached This approach is in the best tradition of the holistic, or psychosomatic, discipline

The tyranny of words interests me deeply, and the criticism of the word "psychosomatic," which Dr Cobb expressed, makes me wonder whether he may not have overlooked a value of this word which is not shared by the word "holistic" The word "holistic," it is true, is of earlier origin and in some respects is more inclusive than the word "psychosomatic" All must agree, however, that the familiarity of the elements in the word "psychosomatic" have made it much more acceptable to members of the medical profession at large and has resulted in a striking increase in the interest paid by the nonpsychiatric members of the profession in the emotional disturbances which accompany all forms of disease It is on the basis of this pragmatic usefulness of the word "psychosomatic" that I should like to register a plea in its favor

I feel that at this point I should rise to the defense of the Navy, since views opposing those expressed in Master's paper, referred to by Dr Cobb, appear in an article by R R Steen, published in the February 1944 issue of the *United States Naval Medical Bulletin,* page 353, in which the author speaks of the effort syndrome as being nothing more than an anxiety state Certain it is that the effort syndrome has an intimate relationship to war If I recall correctly, primitive man used to consider it a good idea to eat the heart of his enemy in order to have his enemy's courage It is evident that these sufferers from the effort syndrome are not planning to have their hearts eaten if they can help it Another striking factor in this syndrome allies itself with my own attitude toward these conditions It may be noticed that all the symptoms Dr Cobb has enumerated are suggestive of an egocentric attitude on the part of the sufferer They represent, in other words, a turning of the patient's attention toward himself This response is typical of the neurotic patient, and I believe all are in agreement that the emotional factors in this condition are of the utmost importance in its genesis

The neurophysiologic aspects of the effort syndrome cannot be neglected, and it is heartening to note the emphasis placed on them in Dr Cobb's paper It is always a good idea to keep in mind that cortical influences on the hypothalamus might well be able to produce all the signs and symptoms of this disorder

My colleagues and I have noticed in our studies on a group of persons suffering from neurocirculatory asthenia that the men in their forties who had had no previous history of heart consciousness but who had been exposed to intense tropical heat exhibited the effort syndrome after some time Coincident with its onset they noticed a loss of libido I wonder, therefore, whether a deficiency of circulating androgens may be a factor in this disorder Dr Cobb mentioned that most of the normal control subjects tried to date the laboratory workers, whereas the group of men with the effort syndrome showed relatively little interest in these girls It seems reasonable to assume the presence of a greater amount of libido in the controls than in the patients I wonder whether Dr Cobb has considered making an androgen-estrogen assay on these patients It is possible that the metabolism of lactic acid is somehow related to the androgen composition of the blood, since athletes in training acquire increased muscle mass and poorly developed adolescents with hypogonadism frequently show a striking increase in muscle mass after androgen therapy

DR FELIX DEUTSCH I should like to ask a question which is chiefly related to the physiologic side I made observations on many hundreds of normal patients Many had a family history of symptoms not only of neurocirculatory asthenia but of heart disease I found that the basal metabolic rate returned to normal much more slowly in such persons than in normal persons The patients who had small arteries did not show a decrease in size of the heart The heart becomes smaller after effort, but the patients showed dilatation of the heart much sooner, and this increase of size persisted longer than in normal persons

Excessive self observation of the heart is a kind of hypochondriasis These patients show a tremendous amount of anxiety, like people who are continually running away from danger, and it is expressed by this kind of reaction of the vasomotor system

DR PAUL I YAKOVLEV, Waltham, Mass I note that, while the symptoms of neurocirculatory asthenia are motivated by emotional factors, they seem to be precipitated mostly on the occasion of locomotion rather than by other patterns of motor activity

DR STANLEY COBB I ought to emphasize that these men can show the syndrome as much on emotional stimulation as on locomotion Locomotion is no more likely than lifting to produce the symptoms

DR ROBERT E JOHNSON To answer Dr Deutsch's question Oxygen deficiency was not measured in these men, and I do not think that the size of the heart was measured before and after exercise

I should like to emphasize a point which Dr Cobb omitted It is the question whether these patients can be trained physically It was apparent that they were in poor physical condition, with poor stamina for ordinary work and for standard tests Everything we measured in them gave values inferior to those for the controls The question whether they would not or could not work was answered to our minds by the fact that even in work which they could endure for the same length of time as normal controls, their performance was worse in every respect An attempt was made to train them in order to see whether they were capable of improvement or fell into the physiologically inferior group In any freshman class at Harvard about 10 per cent are in poor physical condition Of this 10 per cent, a large number can be trained into reasonably good condition, but the state of some remains poor no matter how much they train physically Two groups of 15 patients with neurocirculatory asthenia were subjected under Mr Cox to the same type of training as is given the Harvard freshman Neither cajoling nor threats of Army discipline would induce them to work hard enough to improve Although the experiment was inconclusive, our feeling is that these patients are incapable

of any but slight improvement on training and are intrinsically inferior from the physiologic standpoint

DR DANIEL BADAL With regard to heart disease in the family, there were about 7 per cent with angina pectoris both in the group with neurocirculatory asthenia and in the normal group In some cases we examined the parents of patients Some of these persons had had neurocirculatory asthenia for thirty years, but none had bad hearts Among parents of the control group we found 1 parent with rheumatic heart disease

DR STANLEY COBB Dr Harris spoke of the importance of the emotional state We think that it is extremely important These men were introverts, they had their minds on themselves They were hypochondriac, they had their minds on their hearts because a large number had had the experience in youth of having symptoms referable to the heart and of being warned to be careful of it The overlap of the emotional and the locomotive aspect is exemplified by the case of 1 man in particular I liked him, and it was easy to sit and talk to him In youth he had had trouble after exercise After he was in the Army he had it, but it was much more on the emotional level He was most afraid of inspection In the laboratory we hooked him up to machines for recording respiration, skin resistance and heart rate I had him lie there for five minutes and think about anything he wanted to Then I told him to think about fishing in a river in New Hampshire, and his respiration and heart rate quieted down and his skin resistance fell Then I told him, "You are on inspection, and the officer is coming down the line He is looking at this man and at that man, and pretty soon he will get to you" The respiratory record became irregular and rapid, with big sighs The heart speeded up, and the skin resistance dropped sharply His attack had come on like a conditioned reflex In some subjects it was obvious that they had the attacks because of effort, but they could also have them when they were sitting in a chair or lying in bed

As to androgens, we are working on that now, testing the 17-keto steroids

DR DANIEL BADAL Some patients had been exposed to extreme heat in the tropics and some to extreme cold, as in the Aleutians They mentioned that extremes of heat and cold would bring on the symptoms The two were equally bad

DR STANLEY COBB Of course we had to rule out any men who were convalescent from some recent illness, especially malaria

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PAUL I YAKOVLEV, M D, *Presiding*

Regular Meeting, Jan 18, 1945

Essential Male Homosexuality and Results of Treatment DR ABRAHAM MYERSON and DR RUDOLPH NEUSTADT

By the term "essential male homosexuality" it is implied that this condition is constitutional and is manifest consciously and early in the development of the patient, usually before or at puberty In cases of this condition the male arouses sexual passion and desire, and if there is any capacity for sexual relationship with, and even love for, the female, it is feeble as compared with the desire for the male and is undertaken only to be normal or for social purposes The term "conscious homosexuality" means that there is excluded from the discussion such "homosexuality" as is disclosed by analysis and rests on inference and symbolism

In our previous publication (Androgen Excretion in Urine in Various Neuropsychiatric Conditions, ARCH NEUROL & PSYCHIAT **44** 689 [Sept] 1940), and in Needham's book, the relationship of the male and female hormones, which are present in both sexes, to cholesterol and to each other is shown, and it is obvious from a study of the chemical structure of these hormones that their similarity bespeaks a common origin In previous papers we stated that essential male homosexuality is associated quite constantly with a low excretion of male hormones

and a relatively high excretion of female hormones At that time we pointed out the essential difficulties of reaching this conclusion Time and experience have shown that the conclusion went too far There are many reasons for the failure of experience to corroborate completely our expressed point of view The first is the nonspecificity of the chemical tests for the male and female hormones in the urine, since there are many substances not active hormones which are not differentiated by these tests Furthermore, there are men who are not homosexual who present similar hormonal values In our experience these persons are not normal and in general represent impotent males That the tests have some clinical value, despite their failure to be specific and final in the determination, is shown by the fact that most of the male homosexuals we have studied have shown a lack of androgens and usually an excess of estrogens, both these terms being used to include the nonactive substances which are present

In previous publications we stated that treatment with hormones had been disappointing Wright and, later, Lurie reported success with the use of male hormones in changing the reactions of the homosexual male In the past year one of us has treated 15 persons with essential male homosexuality with a relatively new preparation of the male hormone, a 10 mg tablet of methyl testosterone, to be dissolved in the mouth The present standard dose for these patients is 20 mg, or 2 tablets per day, taken each day for two months, with a resting period of two months This resting period is recommended on the basis of work done by Zondek, in which he showed that antihormonal properties are evoked by the continued use of hormones

The results have been interesting and at the same time puzzling With 2 of these subjects no effect was obtained These 2 men stated that they felt no difference, that their homosexual drive was as consistent and as compulsive as before With the other 13 patients distinct results were obtained, according to the statements of the patients In all of them the homosexual feeling disappeared or became greatly lessened As one man stated, "It was almost as if an antidote had been administered" In only 5 of these patients, however, was a direct heterosexual drive established, and in none of them was it sufficient to bring about a successful heterosexual life In 1 of these patients this result was extremely welcome, since the man was a priest to whom this neutral state was restful In a young boy with pronounced gynecomastia and a severe obsessive-compulsive state, in addition to the driving homosexuality, the drive has entirely disappeared, and he is no longer disturbed by homosexual feelings, although he has, practically speaking, no vivid heterosexual feelings and his obsessive-compulsive state has shown but little change In a homosexual man who became greatly depressed, independently, I think, of his homosexuality, the homosexual feeling disappeared during the depressed stage, just as heterosexual feeling disappears in sexually normal depressive persons As he started to recover, homosexual feelings returned, but they are controllable with the methyl testosterone In a man whose anxiety state seemed related to his complicated social status because of his homosexuality, the administration of the testosterone, by eliminating the homosexual feelings, appeared to do away with the anxiety as well, although this is entirely inference

In all the cases it has been necessary to administer the preparation every two months The treatment is too recent for any definite statement to be made about the future of these patients It does not seem likely, on the basis of past experience with the parenteral administration of hormone and the knowledge gained in this series of cases, that in the adult male homosexuality can be completely cured by use of present day preparations of hormones, although they more easily modify it than does any other form of treatment The failure to cure impotence in males by use of hormones indicates that some other mechanism is involved in the disturbance of direct heterosexual desire in the case of the deviate or sick male

DISCUSSION

DR RUDOLPH NEUSTADT Dr Myerson has pointed out the difficulties with which the biochemical approach to a personality problem, such as homosexuality, is

beset I do not want to repeat his statements, but I should like to stress the close relationship of the various substances with "androgenic" and "estrogenic" activity One is in a precarious situation in that one is not able to differentiate how much of each of these substances is present in a specimen of urine One simply measures the total amount of these substances This, of course, is a great disadvantage, however, I do not expect a real progress in this field for some years On the whole, the biochemical approach to endocrinologic problems, outside of gynecology, has lagged far behind the experimental work In the attempt to approach a psychiatric problem from the biochemical side the difficulties are multiplied One does not know how much the personality affects the formation and excretion of hormones, one knows practically nothing of what different kinds of food, different exercise, swings of mood, sexual abstinence or sexual activity do to the hormone level It is difficult to observe these factors under experimental conditions It is just a matter of impressions, gained by chance observations

The treatment of homosexuality with endocrine preparations suffers from a disadvantage common to all endocrine therapy, i e, the commercial products are not identical with the actual substances present in the organism, nor do they act in an identical manner It is probably a different biologic action, through which Dr Myerson was able to improve his therapeutic results by using methyl testosterone instead of the older testosterone propionate Further modifications may give still better results

Intracranial Aneurysm in Fifty-One Proved Cases DR JAMES L POPPEN

Intracranial aneurysm is one of the most deadly conditions affecting the intracranial cavity and has been treated by most neurosurgeons in the past by watchful waiting In recent years Dandy has stimulated consideration of actual surgical intervention by either direct or indirect attack on the aneurysm and has demonstated that it is a condition which can in many instances be cured by surgical means Symonds (*Guy's Hosp Rep* **73** 139 [April] 1923) should receive considerable credit for emphasizing the history and physical manifestations produced by intracranial aneurysm

The etiologic factor in intracranial aneurysm is predominantly congenital Several excellent reasons for their development have appeared in the literature Fetterman and Moran found that the circle of Willis was like that described in the anatomic textbooks in less than 50 per cent of cases Many variations and anomalies were observed, involving mainly the posterior communicating artery Glynn noted that the elastic tissue was predominantly concentrated in the internal elastic lamina rather than being uniformly distributed throughout the media and adventitia, as in other arteries of the body Bremmer suggested that stimulation of the growth of the walls of the blood vessel by mechanical pulsations inside the artery and the resulting change in angulations of arteries, which in the embryo are acute and later become almost right angles during the developmental stage, are factors in producing congenital weakness at the bifurcation He stated the belief, also, that the transitional remnants of vessels, having little pulsation, are therefore particularly vulnerable to development of aneurysm This opinion is also entertained by Dandy

Syphilis played no part in the formation of aneurysm in the 51 proved cases That syphilis was a relatively unimportant cause was indicated as well by Dandy's series and by the 1,023 collected cases of McDonald and Korb In 10 of our cases the aneurysms occurred in patients with hypertension and associated arteriosclerosis That trauma plays no part, or only to a slight degree, in causing either the aneurysm or the rupture of aneurysms is emphasized by the study of Magee in 150 cases The condition predominates in the female (34 females, 17 males in the present series) The right side was involved in 18 cases and the left in 33 cases The diagnosis is made from the history and clinical signs The classic picture is that of periodic bouts of unilateral headache or unilateral neuralgic pain in the face, eye and forehead The actual rupture is manifested

by the classic signs of subarachnoid hemorrhage The larger aneurysms involving the internal carotid artery may show signs of tumor in the region of the sella turcica Roentgenograms of the skull show changes only when the aneurysm has reached such a size that it erodes bone in the region of the sella turcica and is manifested by unilateral destruction of the clinoid process and upward displacement of one of the anterior clinoid processes In a few cases crescentic calcification makes the diagnosis of aneurysm almost certain However, other tumors may have similar calcification and be mistaken for aneurysm Seventy-five per cent of intracranial aneurysms involve the anterior two thirds of the circle of Willis The internal carotid artery and the middle cerebral artery seem to be the most vulnerable, although the anterior cerebral artery is also commonly involved

It is unfortunate that the symptoms of an intracranial aneurysm in many instances are initiated by a spontaneous subarachnoid hemorrhage Magee found that 52 of 150 patients with subarachnoid hemorrhage died during the primary attack Fifty of the 98 survivors of the first attack had a recurrence, and 32 more failed to recover, indicating the seriousness of the entire situation

It is evident that actual surgical attack can be intelligently applied only in patients with typical histories and clinical signs However, in the surgical attack, it is of value to know the exact location of the aneurysm, as well as its origin Decision can then be justly made as to whether the aneurysm can be trapped between ligatures with reasonable safety or whether it must be attacked indirectly by ligation of the large vessel in the neck to avoid making the patient a hopeless cripple after operation In many patients there are no focal signs It is logical, therefore, to visualize the arterial tree intracranially, and since no untoward results have been noted, either at the time of injection or later, with thorotrast, we feel that it is indicated for accurate location of the aneurysm, and thus as an aid in the decision as to treatment Also, its use has assisted in making the diagnosis definite

Before surgical intervention, it is important to determine whether the collateral circulation on the side on which the aneurysm is located is adequate and whether there are any anomalies This can be done by compression of the carotid artery, the pressure being applied over the great vessels in the neck and graduated so that the patient is able to tolerate complete compression for ten minutes three times a day The compression also helps in determining whether the patient has an irritable carotid sinus which may cause untoward signs, which may be erroneously interpreted as indicating that the patient is unable to tolerate compression

Direct attack and excision of the aneurysm itself are, of course, the procedure of choice if indications are that it will not leave the patient a permanent cripple The indirect attack by ligation of the common or internal carotid artery is then the only alternative Partial ligation of the arterial flow through the internal carotid artery can be accomplished by ligation of the common carotid artery, which cuts down only 50 per cent of the blood supply to the internal carotid artery It more complete occlusion can be tolerated, the internal carotid artery itself can be ligated If the internal carotid artery cannot be safely ligated, the common carotid artery, as well as the external carotid artery, can be ligated, leaving the superior thyroid and lingual arteries intact, so that they allow collateral circulation into the internal carotid artery

After ligation it is important to keep the patient in the Trendelenburg position in an oxygen tent, so that the blood which does enter the cerebral hemisphere is well oxygenated The patient must be carefully watched If late unilateral symptoms appear, heparin is given immediately to prevent ascending thrombosis or embolism

Slides were shown to demonstrate the various characteristics of aneurysms involving the internal carotid, the middle cerebral and the posterior communicating arteries Slides were also shown of two aneurysms that had been completely extirpated

DISCUSSION

DR CHARLES KUBIK I have been much interested in Dr Poppen's paper and the lantern slides of his unusually clear arteriograms Several years ago Dr Ayer and I went over the records of a group of cases of spontaneous subarachnoid hemorrhages—most of which, one may assume, were due to leaking or ruptured intracranial aneurysm—and found the mortality not nearly so high as that given by Dr Poppen I think that it was 28 per cent for all patients with spontaneous subarachnoid hemorrhages admitted to the hospital I know of no follow-up report on a large series of cases over a long period, though all know patients who have recovered, without operation, and remained asymptomatic for ten years or longer It seems to me that the results of both medical and surgical treatment in larger groups of cases for longer periods will have to be analyzed before a comparison of the two methods of treatment can be made There is, of course, no doubt of the benefit derived from operation when it provides relief of pain Dr Poppen's results, with respect to complications which may follow ligation, have been surprisingly good

DR D DENNY-BROWN I am glad Dr Poppen has emphasized the seriousness of intracranial aneurysm Perhaps arterial ligature is not advised as often as it might be It appears to me that the most serious subarachnoid hemorrhage arises frequently from aneurysm of the anterior communicating artery when the side of the lesion is in doubt, or from the junction of the posterior communicating and the posterior cerebral artery Further, it is my impression that the most dangerous aneurysms are quite small The period of difficulty in decision is soon after a leak Has Dr Poppen found any evidence that thorotrast damages vascular endothelium, and would he advise its use to localize the aneurysm in such an early stage? What would Dr Poppen consider to be a contraindication to arteriographic examination?

DR PAUL B JOSSMANN I should like to ask Dr Poppen whether he has had experience with the further development of aneurysms after ligation, particularly with respect to their pathologic changes I wonder whether, by establishment of collateral circulation, retrograde refilling of the aneurysm takes place after a certain period

DR ABRAHAM MYERSON I should like to ask Dr Poppen to give us more details of his injection of thorotrast When I was using the method, I did not get such beautiful pictures

CAPT JAMES C WHITE (MC), U S N R As far as arteriovenous aneurysms are concerned, the results which my associates and I have had with ligation of the common carotid artery have been discouraging Of 6 cases of this type, bruit recurred in 3 and hemiplegia developed in 1 From this experience I do not see how ligation of even the common carotid artery can be considered a really safe procedure The case of complicating hemiplegia was in a woman of 40, who tolerated thirty-six hours of preliminary occlusion with a band of fascia around the common carotid artery The second day we reopened the incision and cut the previously occluded artery between two ligatures Hemiplegia developed during the night, twelve hours after the second, and final, ligation

DR H HALE POWERS, Wellesley, Mass I should like to ask about the age when the initial hemorrhage occurred in the patients Has Dr Poppen any data as to what effect on mental capacity ligation has had?

DR WILLIAM JASON MIXTER Captain White knows more about this than I do I think it is a beautiful piece of work, and I am particularly interested in the excellence of the roentgenograms which he has obtained He leads the way, and even if our statistics have not been as good as his, we should follow his lead and endeavor to improve our results

DR JAMES L POPPEN My associates and I have used thorotrast in small amounts, using 10 cc for the stereoscopic film We have seen no early or late

effects from its use The ability to obtain stereoscopic pictures of the aneurysm can be accomplished only by enthusiastic and intelligent assistance of the x-ray department We are fortunate in having the cooperation of Dr G A Marks, of the New England Deaconess Hospital, and his group of technicians have helped me tremendously Dr H F Hare and his technicians at the New England Baptist Hospital have been equally helpful There is no reason that excellent films cannot be obtained if there is intelligent cooperation between the x-ray technicians and the surgical team I see no contraindication to ligation of the large vessel in the neck in a patient who has a large aneurysm as long as one knows that he is able to tolerate occlusion of the vessel, and this can be done by watching the patient under local anesthesia at the time of the contemplated ligation If the patient is able to tolerate occlusion for at least one-half hour, one can assume that it is safe to ligate This rule, of course, is not absolute One must continue to watch the patient even after he has been returned to the ward to be sure that no hemiplegia takes place

In answer to Dr Jossmann, it is my impression that whenever the direct pulsations on the aneurysm can be diminished, there is less danger of rupture

In regard to Captain White's patients in whom hemiplegia developed after ligation of the common carotid artery, I feel that this tragedy can be avoided by the use of dicoumarin (3,3-methylene-bis-4-hydroxycoumarin) and heparin Use of the dicoumarin may be started on the second postoperative day It certainly should prevent ascending thrombosis Whether it actually would avert an embolus I am uncertain, but I believe the chances of the development would be definitely less Certainly, if hemiplegia develops after ligation of the common carotid artery, it will also develop after ligation of the internal carotid artery, so that I cannot see why the common carotid artery may not be attacked surgically, since it reduces the blood supply to the brain only 50 per cent in most cases

The initial hemorrhage occurred at no particular age in our patients The youngest patient was 15 years of age and the oldest 69 There has been no effect on the mental capacity following ligation to date We have had no operative deaths, however, complete hemiplegia resulted from ligation of the internal carotid artery in 1 case

News and Comment

ALFRED ULLMAN LABORATORY FOR NEURO-PSYCHIATRIC RESEARCH

The Sinai Hospital, of Baltimore, announces the establishment of the Alfred Ullman Laboratory for Neuro-Psychiatric Research The work in the laboratory will be carried out under the direction of Dr H S Rubinstein

AMERICAN SOCIETY FOR RESEARCH IN PSYCHOSOMATIC PROBLEMS

The annual meeting of the American Society for Research in Psychosomatic Problems will be held at the Hotel Pennsylvania, New York, May 11 and 12 1946 "Contributions of Military Medicine to Psychosomatic Medicine" will be discussed in the morning and "Psychosomatic Aspects of Orthopedic Practice" in the afternoon of the first day After the annual dinner an illustrated parody on "New Advances in Psychosomatic Investigative Technics," by Dr Bertram D Lewin, will be presented On May 12 there will be volunteered contributions

Because of space limitation, reservations should be made at least two weeks prior to the meeting Further information may be procured from Dr Roy G Hoskins, chairman, program committee, 714 Madison Avenue, New York 21

Book Reviews

Experimental Catatonia A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology By Herman Holland de Jong, M D , with forewords by Nolan D C Lewis, M D , and David T Smith, M D Price, $4 Pp xlv, plus 225, with 15 tables and 38 figures Baltimore Williams & Wilkins Company, 1945

Since the discovery by the author in the 1920's that bulbocapnine was capable of reproducing the motor phenomena seen in catatonia, de Jong has pursued his researches with a number of collaborators and in various localities The present work is an extension of the investigations published with Baruk (*Rev neurol* **2** 532, 1929) De Jong has found that, far from being a specific effect of bulbocapnine, catatonia is a general reaction form attributable to disturbances of function of the central nervous system and that it may be produced by a wide variety of chemical and physical methods Many drugs have been tested under varying circumstances, and the author has shown that in many instances, in the twilight zone between life and death produced by the administration of slightly sublethal doses, the animal responds with catatonia It may be significant that a still higher dose provokes convulsive seizures, sometimes eventuating in death Anoxia almost certainly plays a part in the genesis of the symptoms, because they may be elicited by experiments leading to anemia, anoxemia and other deleterious influences on the central nervous system Centrifugation, electronarcosis and cerebral resection may also induce catatonia Chilling and heating would seem to be worth investigating

One misses in this volume a consideration of the effects, particularly the psychologic ones, that are induced in man by the administration of bulbocapnine to normal and "precatatonic" persons A tantalizing glimpse is given of the exaggerated effect of bulbocapnine in animals who have undergone small or large cortical extirpations

De Jong reports on a number of blind alleys For instance, the urine of certain schizophrenic patients contains a substance that is capable of producing catatonia in mice After laborious research this substance was finally identified as nicotine and was found to be present in considerable amounts in smokers, but not in those who were not exposed to tobacco The role of histamine held promise for a time, but further researches ruled out this substance as an important contributing factor

The author is somewhat overly generous in detailing technical methods and protocols These seem to belong, rather, in briefer papers, where investigators who wish to tread in his footsteps may find them The book makes more fluent reading if these are skipped, since the conclusions of each experiment are briefly stated The author is particularly to be commended for the clarity with which he has pointed out phenomena other than waxy flexibility by means of which the catatonic state may be recognized His classification of the phenomena characteristic of catatonia is as follows

A Hypokinetic phenomena
  1 Diminished motor initiative
  2 Catalepsy
  3 Negativism
    (*a*) Passive
    (*b*) Active
B Hyperkinetic phenomena
C Autonomic phenomena

Two tests of particular value for the demonstration of catatonia in man are described, one to bring out a latent catalepsy and the other to test for passive negativism The patient kneels on one chair and rests his hands on another,

then the chairs are gradually separated and the patient is "drawn out," and may remain in this position for a considerable period In the test for passive negativism, the examiner faces the patient, standing, and without saying what he intends to do slowly rotates the shoulders of the patient 180 degrees or more If the patient fails to move his feet adequately to compensate for the changed posture, the reaction to the test is positive Active negativism is noted if the patient when pushed in a certain direction takes several steps in the opposite direction, in passive negativism he may be pushed *en bloc* and remains in the final position

De Jong seems to be on safer ground when he relies on these tests than when he includes "diminished motor initiative" among the characteristic signs of catatonia Also, the hyperkinetic phenomena are observed in states other than catatonia Both these conditions seem to have a fairly definite relation to the functioning of the frontal lobe, but de Jong's experiments do not show that the syndrome of catatonia may be evoked by lesions of the frontal lobe

New Directions in Psychology Toward Individual Happiness and Social Progress By Samuel Lowy, M D Price, $3 Pp 194 New York Emerson Books, Inc, 1945

This book, written primarily for laymen, is concerned with one of the major problems facing the world today, namely, the "cultural lag" between modern scientific doctrines and the woefully inadequate use which society makes of them Using the informal essay style suitable for a nonprofessional reader, Dr Lowy has written a series of short articles urging the application of modern psychologic technics to social reconstruction His thesis is that the "core of the social problem is the element of aggression in its various aspects and manifestations" The author uses chiefly freudian concepts, with occasional reference to other psychologic systems

Dr Lowy attempts to cover a wide range of topics, varying from politics to marriage, education and religion In a brief chapter, entitled "Suggestions on General Reform," he advocates a rather nebulous state combining the best features of both communism and democracy without any of their weaknesses This makes interesting reading but is hardly practical at present, and the subject is dealt with on a very superficial plane There are certain deficiencies in structure and style which detract somewhat from the effectiveness of the book Since much of the subject matter is controversial in essence, the parenthetic and apologetic asides which the author intersperses throughout the text serve only to increase the reader's uncertainty in attempting to clarify the issues in his own mind In addition, the author, in his preface, advises the reader to turn to the "Closing Remarks" first, whereas it would have been more logical to label these "Opening Remarks," placing the text before the first chapter

Despite these minor weaknesses, the book is stimulating, and Dr Lowy writes with obvious sincerity and enthusiasm It is recommended particularly to psychologists, sociologists, educators and enlightened politicians who are interested in the betterment of human relations through a fuller understanding of mental processes

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CHANGES IN SENSORY ADAPTATION TIME AND AFTER-SENSATION WITH LESIONS OF PARIETAL LOBE

COMMANDER M B BENDER, MC(S), U S N R

PATHOLOGIC conditions frequently produce symptoms which are reflections of normal functions This has been affirmed repeatedly by various authors One of the normal functions which has thus been elicited in patients with injuries to the brain is rivalry with resultant dominance of strong over weak sensation The process of rivalry with resultant dominance was recently demonstrated in patients with defects in the visual and cutaneous spheres [1] Visual perception, diminished in a given area owing to a lesion in the optic pathway, can be further reduced or made totally extinct when stimuli (objects) are exposed simultaneously in the normal and in the affected field of vision This visual extinction was explained by Poppelreuter as due to inattention [2] However, a careful study of patients manifesting this phenomenon has thrown doubt on Poppelreuter's theory, for several reasons (*a*) The extinction occurs in spite of the patient's attempt to concentrate on the object in the affected field (*b*) The phenomenon is sometimes found to be limited to homonymous quadrants Certainly, it would be difficult for one to lose attention in one and not in the other quadrant of a homonymous half-field of vision (*c*) The extinction is sometimes incomplete, being manifest in the form of a reduction of visual perception This reduction may range from fluctuation to almost complete obscuration of the exposed image, the amount depending to some extent on the degree of stimulation in the normal field of vision The fact that some visual

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1 (*a*) Bender, M B, and Furlow, L T Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch Neurol & Psychiat **53** 29-33 (Jan) 1945 (*b*) Bender, M B Extinction and Precipitation of Cutaneous Sensations, ibid **54** 1-10 (July) 1945

2 Poppelreuter, W Die psychischen Schädigungen durch Kopfschuss im Kriege 1914-1916 Die Storungen der niederen und hoheren Sehleistungen durch Verletzungen des Okzipitalhirns, Leipzig, Leopold Voss, 1917, vol 1

perception is preserved in the affected field indicates that the patient is paying attention The indistinctness of the exposed image must therefore be due to other factors (*d*) The phenomenon is not present with very rapid exposures of the objects in both fields of vision In fact, in these circumstances the patient may actually see more than his plotted field of vision would indicate [3]

Similarly, studies in cutaneous perception with the method of double and simultaneous stimulation may reveal varying degrees of reduced sensibility on the affected side, whereas single stimulation may show no such reduction [1b] Again, under these conditions there is a variety of alterations in cutaneous perception which seem to form a continuum from an elevation of threshold through fluctuation, dulling and reduction of adaptation time to complete abolition of sensation Here, too, it would be difficult to account for the reduction or extinction of cutaneous perception on the basis of inattention All these observations seem to refute Poppelreuter's hypothesis To be sure, attention is a factor in the ability to perceive Newhall,[4] in controlled experiments, found that the closer the attention the better discrimination there is between faint visual stimuli Furthermore, Hardy, Wolff and Goodell [5] asserted that distraction, attitude and suggestion may modify the threshold for pain

Besides the mechanism of rivalry with resultant dominance of one sensation over another, there are other processes which participate in the elaboration of a sensation or percept Sensory adaptation and after-sensation are two such processes, which will be considered in this communication

Psychologically speaking, sensations in nearly all modalities show the phenomenon of negative adaptation That is, under continual and unchanging application of a given stimulus the characteristic sensation evoked disappears after a given interval This interval is known as the sensory adaptation time

As used in this paper, the term "adaptation" is taken from the language of the experimental psychologist It is realized that the psychologist tends to analyze sensory adaptation in terms of function within the peripheral end organ Similarly, the physiologist tries to relate adaptation at the receptor level to the refractory stages in conduction of nerve fibers [6] However, it is difficult to interpret a subject's report of changes in perception (adaptation) from the standpoint of the peripheral

3 Bender, M B, and Teuber, H L Phenomena of Fluctuation, Extinction and Completion Associated with Visual Perception, Arch Neurol & Psychiat, to be published

4 Newhall, S M Effects of Attention on the Intensity of Cutaneous Presence and Visual Brightness, Arch Psychol (no 61) **9** 1-75, 1923

5 Hardy, J D, Wolff, H G, and Goodell, H The Pain Threshold in Man, A Research Nerv & Ment Dis, Proc (1942) **23** 1-15, 1943

end organ alone In response to a stimulus all levels of the nervous system are activated, and the cortex must be considered as one of the substrates in which adaptation occurs In this communication, therefore, adaptation is used in an empiric (clinical) sense, that is, the patient's reports of the presence or absence of a given sensation are recorded verbatim When the patient states that he no longer feels a given stimulus, it is implied that adaptation is complete Although adaptation of necessity involves the peripheral level, the pathologic material to be presented here illustrates the less explored role played by the cerebral cortex

Closely related to the adaptation mechanism is the phenomenon of after-sensation After-sensation is a reaction found on the removal of a cutaneous stimulus and is analogous to the visual after-image As a rule, an after-sensation lasts a few seconds, the duration depending on the intensity of the stimulus applied Often it is not recognized unless the subject's attention is called to it The duration of the after-sensation varies from one person to another, but there is no notable difference between corresponding points on the two sides of the body

Alterations, especially reduction in sensory adaptation time, are commonly found in persons with defective sensation In a large series of patients with battle wounds involving various parts of the sensory nervous system (observed at a Naval hospital during 1944), special studies on sensory adaptation and after-sensation were made In evaluation of changes in sensory adaptation and after-sensation in the affected area, the normal zones were compared as a control Nearly all these patients exhibited a reduction of the adaptation times for pain, touch and temperature sensations [1b] After-sensation was also diminished or abolished The most pronounced reduction in adaptation time was apparent in cases in which there were lesions of the parietal lobe In 1 patient this was so extreme and involved so many modalities that it caused him discomfort and, at least in one instance, embarrassment

REPORT OF CASES

CASE 1 [7]—A Marine aged 29 was wounded in the right side of the head but was not incapacitated until a missile struck him in the left occipitoparietal region, when he fell unconscious On regaining consciousness, he found himself in a dugout, unable to speak or to move the right side of the body He was evacuated to the hospital On examination, global aphasia, right hemiplegia and apparent hemianopsia were noted One week later the hemiplegia had disappeared A craniotomy was then performed, and fragments of bone were removed from the left side of the head The underlying occipitoparietal cortex was

6 This school of thought is represented by Adrian (Adrian, E The Basis of Sensation, New York, W W Norton & Company, 1928)

7 This case was previously described from the standpoint of visual extinction [1a] Some of the content is therefore to be repeated in this report

contused The patient continued to improve Within a month the hemianopsia began to recede, and he became more communicative However, the following significant symptoms lingered during the next two months (*a*) striking acalculia, (*b*) spelling defect, (*c*) dysgraphia and (*d*) inability to perceive an object on the right when a concomitant stimulus was present in the left field of vision Spontaneous speech returned He showed little agrammatism and no anomia There was no finger agnosia or disorientation for right and left His greatest defect was in calculation He had always considered himself good in arithmetic, but twelve weeks after the injury he still was unable to recite the multiplication tables of 2's and 3's accurately He made errors in simple tests, such as 8 + 3, and other sums which equated to less than 20 The defect in calculation was greatest for subtraction Often he was unable to recognize the correct solution to the problem, even when it was given him, and he was seldom certain of the answer

Visual Disturbances—Ever since the hemianopsia had begun to recede, the patient complained, "If I stare long enough, my vision starts to blur on the right side I can't go to the picture show for the same reason When I first start to read, everything is clear, but then I must stop because the right side blurs After a rest I can see again Also, if I look at one object long enough and look away, I still can see it" The last phenomenon was present for one month Examination revealed that the patient was unable to see in the right homonymous field when an object was exposed simultaneously in the left field of vision This was true with both uniocular and binocular testing When the perimetric fields became normal (the last defect noted was that for color in the right inferior quadrant), this phenomenon became most apparent While he was fixing on a central point, the patient clearly perceived the form and color of an object placed in the right field of vision However, when another object was brought into view on his left side, the image on the right became extinct This extinction phenomenon was noted on repeated examinations in the right homonymous fields of vision During the extinction of the image the patient made a strong effort to "see" the object by squinting his eyes and concentrating but was unsuccessful. However, as soon as the stimulus in the left field was removed, he perceived the exposed object on the right When tested for separately, the object on the right appeared clear but sometimes blurred and dull The object seemed to fluctuate in distinctness

In time the remaining aphasic symptoms decreased further, although the acalculia was still striking The visual phenomenon began to change Fourteen weeks after the injury it was noted that the image in the right field did not always vanish when the left field was stimulated Instead, it became dull, lost its form and color and appeared shadowy There was no micropsia or teleopsia Again, when the stimulus in the left field of vision was removed, the object on the right became more luminous and regained its color and meaning This was noted irrespective of the degree of likeness or unlikeness in luminosity of the objects exposed in the opposite fields of vision There was no apparent loss of attention What there seemed to be was a relative reduction of visual acuity or a dimming of the visual image These phenomena were less apparent the nearer the object in the right field was exposed to the point of fixation

Sixteen weeks after the injury the following observations were noted (*a*) On separate tests of all four quadrants, the patient stated that the image in the right superior homonymous field of vision was clearer than that in the right inferior homonymous field (*b*) The dimming of the image was much more apparent in the inferior than in the superior quadrant on the right side Thus,

when a pencil was placed in the patient's right inferior field, he recognized it, but when another pencil was placed in the left inferior field, the one on the right became blurred, dull and shadowy The same was true when the corresponding superior quadrants were tested, but the difference here was much less apparent than in the comparable lower quadrants When a long pencil was held vertically in the right field of vision, the patient stated he perceived that part of the pencil in the upper quadrant more clearly than the portion in the lower quadrant The simultaneous exposure of an object in the same position on the left side produced a further decrease of perception on the right side, particularly in the lower quadrant

Sensory Disturbances—Five months after the injury the patient returned from a forty day furlough and complained that he did not know what his right hand was doing He described the following embarrassing situation "I was sitting in the parlor with my right hand around my girl Her mother was sitting opposite us Suddenly I noticed a change in the mother's facial expression She seemed uneasy and disturbed by something So did my girl When I looked to the right, I found that my right hand had dropped down to the girl's breast I quickly straightened out and apologized At the same time, I could not understand how it happened that I was not aware of my hand Since then I have tested myself and find that I lose feeling in this hand very quickly It goes dead If I look at it, or if I make a strong movement, then the feeling in the hand comes back Sometimes, I think I have only one hand" [8] Subsequently, he became more conscious of this symptom in other forms Thus, when he reached for a tray of food, he almost tore his pocket open because he was unaware of the fact that his right hand was in the pocket This loss of awareness of the right hand recurred frequently Sometimes, he unconsciously dropped a cigaret which he held in his right hand Not infrequently he was surprised to find this limb in a position which he could not recall having assumed When he hesitated for several seconds while writing, he found that he could not feel the pencil in his hand unless he looked at it For this reason, he could not write legibly If he did not scrutinize them carefully, the lines which he wrote became crooked, even on ruled paper

Sensory Examinations [9]—Pain Sensation of 2 5 to 15 Gm weights with a no 10 needle point applied to different areas of the skin seemed to be preserved on the right side when tested for separately and compared with sensation on the left However, when the left and the right hand were stimulated simultaneously, he felt pain more keenly on the left side On the right side the sensation of pain disappeared rapidly, and during this phase it fluctuated in intensity It then changed to a

8 It is interesting that the patient became aware of trouble with his right hand during an embarrassing situation This suggests that the new symptoms were psychogenic (conversion phenomena) Psychiatrically, it might be argued that the patient freed himself of all blame for the parlor incident by accusing his formerly paralyzed hand of doing things without his knowledge Although one cannot deny that the accidental shifting of his right hand to the girl's breast was due to a subconscious libidinal force, subsequent neurologic and special studies will reveal that his act was most probably the result of organic defects in sensation (reduction of adaptation time with consequent impairment of kinesthesis) Nevertheless, it was emotional stress which precipitated the latent sensory defects The case illustrates the close relationship between the psychogenic and the organic components of symptoms

9 The method employed in eliciting the sensory status was the same as that described in a previous communication [1b]

sensation of pressure and ultimately disappeared altogether The time for the disappearance of a sensation produced by a 5 Gm needle point stimulus was 12 seconds on the right hand and well over 70 seconds at the corresponding point on the left hand Foci on the rest of the right upper extremity showed similar reductions of sensory adaptation time, but the reduction was most pronounced in the distal portion A slight decrease in adaptation time was also noted over the trunk and the lower extremity on the right side[10] After-sensation for this modality was either absent or much diminished on the right side of the body, especially in the hand

Temperature Sensation The adaptation for temperature sensation was much reduced in the right hand Thus, when identical objects were held in the hands, with the hand on the right he perceived a change in temperature within 5 to 7 seconds, while with the left hand he did not sense a change until after 15 seconds

When both hands were placed in warm water (115 F), the sensation of warmth or heat rapidly disappeared (within 5 seconds) in the right hand, whereas it lingered for a long period in the left hand The change occurred first at the wrist and spread to the finger tips The temperature sensation disappeared last in the right index finger At the time the sensation of heat became extinct the sensation of wetness disappeared In fact, after 10 seconds the patient was uncertain whether his right hand was in the bowl of water at all when his eyes were closed

Touch and Deep Pressure Sensation The adaptation time for superficial touch as well as deep pressure sensation was much reduced in the right hand, the sensation disappearing completely within 5 to 10 seconds The sensation on the left side lasted from 30 to well over 80 seconds These changes were well illustrated by the tests made for stereognosis

Stereognosis The patient immediately recognized the shape, size and texture of any object placed either in the right or in the left hand or simultaneously in the two hands With his eyes closed he felt and correctly identified a pencil held in his right hand, but when he held the pencil still, it seemed to him to have disappeared after an interval of 7 seconds The same was true for larger and heavier objects, such as a comb, a fork and a box of matches The duration of the "adaptation time" for these was longer than for lighter and smaller objects[11] Stereognosis in the left hand was normal, and he could recognize the presence of an object even after holding it for over 3 minutes

Barognosis Weights were easily differentiated when placed in each hand separately or in the two hands simultaneously, but after a few seconds barog-

10 Since the patient's sensory complaints were confined to the right hand, most of the special tests for adaptation time were made chiefly on the right limb and the results compared with those for the left Differences in pain sensation between the two sides of the body were found elsewhere, but since these were not conspicuous, similar tests for other modalities were not made in every part of the body to the same extent and in the same detail as for pain Henceforth, comparisons made in places other than in the hand will not be reported unless the changes found were significantly different than those reported for pain sensation

11 It is fully realized that one cannot speak of a true adaptation for stereognosis or other complex perceptions with the same connotation as for simple pain or pressure sensation The probability is that adaptation for the primary modalities took place first, and once these sensations disappeared the patient could no longer perceive the object held in his hand Nevertheless, it is possible that there may be adaptation for the stereognostic sense per se

nosis became defective in the right hand Identical (480 Gm) oblong weights placed in each hand felt the same, but after a few seconds (table 1) there was a change The object on the right became lighter than that on the left, and later the sensation of its presence seemed to have disappeared altogether Not only did the object seem to vanish, but his hand and forearm felt as though they were not there

When this experiment was repeated and continued for a much longer period, the patient showed the same reactions At the end of 3 minutes, although he had no sensation of a hand, of a forearm or of the weight which he held, he began to notice a peculiar pulling pain in the elbow region, "as though the cords were pulling there" This was the first subjective sign of fatigue in the right upper extremity in contrast to the left hand, which began to tire 2 minutes after the weight had been put on.

Kinesthesia As already mentioned, the patient complained of loss of sense of position of the limb in space after a relatively short interval Recognition of

TABLE 1—*Time Elapsed After 480 Gm Weights Were Placed Simultaneously in the Hands with the Patient's Eyes Closed*

Time, Sec	Right	Left
7	Sensation is decreasing	Stereognosis and other sensations preserved
19	Patient barely feels touch or outline of square weight in hand	No change
37	Hand seems to have disappeared	Hand is felt in outstretched position
40	Weight is lighter in right than in left hand, sensation of weight is felt at wrist and elbow, rest of extremity is not felt	No change
65	No sensation of temperature, right hand moved up spontaneously above left, weight is lighter than that in left hand	No change, possibly left hand is moved down lower than right, patient is not aware of difference in position of outstretched hands, which is about 4 inches (10 cm)
120	Patient is unable to determine shape or size of weight, no sense of fatigue as yet, weight feels lighter than that on left hand even after patient looks at object and moves it up and down	Patient still can recognize object with left hand, which feels tired and heavy at wrist and elbow

initiation of movement or passive motion was normal throughout The sense of position of a digit, the forearm or arm or of parts of the lower extremity in space was also found to be normal However, once the finger or any other part of the upper extremity had assumed a given posture and the patient was instructed to close his eyes and not to move his limbs, the ability to recognize the fixed posture or position in space of the right hand was lost after 7 seconds or more Thus, when he held both upper extremities in the extended position above the head, after 7 seconds he complained that the feeling was "leaving" in his right arm and that this peculiar awareness of the absence of the limb spread distally toward the forearm within 10 to 12 seconds Finally, he felt the absence of the right hand and forearm and said it was a sensation "as if they were not there"

On raising both feet in the air with his eyes closed, he noted after an interval of 10 seconds that the left lower extremity was still there but that he hardly felt the presence of the right leg and foot He realized that the foot was there, but only because there was the weight of the shoe (Symptomatically, the patient complained of frequent tripping with his right foot)

On occasions when he was distracted by a conversation, he was suddenly asked to describe the location and posture of the right upper extremity without moving or looking at the affected limb He then found he could not locate or describe the posture of the right arm, forearm or hand He realized he possessed an arm and hand, but he could not locate them in space Once, he thought the extremity was elevated to table level, but actually it was hanging limply at his side, his left arm was raised, and he identified this correctly Initial two point discrimination and vibration sense appeared to be intact

Graphesthesia This modality was impaired in the right hand when the left hand was simultaneously stimulated with a painful stimulus In fact, with simultaneous double stimulation on the two sides of the body and at corresponding points, almost all modalities showed a reduction in adaptation time on the right side, especially in the right upper extremity This reduction was more conspicuous than the results obtained with single stimulation

Spontaneous arm movements were diminished on the right Although the patient was right handed, he invariably pointed and gesticulated with, and seemed to prefer, his left hand in everyday activity The motor power was normal

The patient was studied for several months He continued to show this reduction in adaptation time for almost all modalities, especially in the right upper extremity He was discharged from the service, and when he wrote one year later he reported no change in his subjective status

Comment.—This case illustrates at least three mechanisms which participate in perception under pathologic conditions (*a*) rivalry and dominance (manifested by the phenomenon of visual extinction), (*b*) adaptation to sensory stimuli (made apparent by reduction of adaptation time and consequent disturbances in cutaneous and kinesthetic perceptions) and (*c*) dynamic organization of body sensations into a scheme (particularly evident when his sense of position of a limb in space became defective as a result of reduced adaptation time) *Pari passu* with reduction in adaptation time, there were a loss of sense of position and a gain of the illusion that a limb was missing [12] Evidently, the patient had a

12 Head (Studies in Neurology, London, Oxford University Press, 1920, pp 779-789), in his studies on sensation, described several cases in which the patient complained of a sensation of missing part of a limb One of them, with a gunshot wound implicating the left frontal and parietal lobes, complained two years after the injury that when he awakened at night he sometimes felt as though the last three fingers of his right hand were missing, that the whole hand seemed to disappear and that he had to move the fingers to make them "come to" again Another patient, with a bullet wound of the right parietal cortex, complained three months after the injury that when he awakened at night he felt as though he had lost two or three fingers and that it seemed as though "this part of the left hand was gone altogether" Although these cases are not ideal examples of reduction in adaptation time, they illustrate a form of autotopagnosia, probably due to impairment of kinesthesia The fact that movement caused return of sensation of a limb suggests that the disturbance in the body image in these cases was the result of an altered adaptation mechanism

disorder in the body image or postural model of the body [13] The disturbance in body scheme was transient and reversible It appeared only when sensation in general became defective as result of impairment of the adaptation mechanism and disappeared whenever he moved, touched or looked at the affected limb [14]

Underlying most of the sensory (cutaneous and kinesthetic) disturbances was the reduction of adaptation time These changes were probably not due to fatigue, because (*a*) the removal of a stimulus from a cutaneous focus which became insentient with adaptation sometimes evoked an after-sensation and (*b*) the immediate reapplication of a stimulus at the same focus was quickly appreciated

All the symptoms were most profound in the right upper extremity, especially in the distal portions They all became manifest only after an interval which corresponded to a reduced adaptation interval

The decrease in adaptation time became more apparent with simultaneous double stimulation Some sensory disturbances were frequently found in patients with lesions of the parietal lobe, particularly on bilateral stimulation, but rarely to the degree found in this patient Evidently, lesions of the parietal lobe can reduce sensory adaptation time

Associated with a reduction in adaptation time in these patients was a decrease or abolition of the after-sensation [1b] A decrease in after-sensation per se did not seem to produce symptoms These patients had no complaints in that respect

As already mentioned, not all patients with disease of the cortex and sensory pathways showed a decrease in adaptation time or in duration of after-sensation Some of them showed what seemed to be an increase Prolongation of after-sensation was often marked and more conspicuous than increase in duration of adaptation With these changes there was usually an increased sensitivity to painful stimuli, and this was the chief basis for the patient's complaints

The following case is illustrative of changes in after-sensation and adaptation time in a patient with injury to the anterior portion of the parietal lobe

Case 2—A 22 year old Marine, private first class, sustained a gutter type of bullet wound in the left superior frontoparietal area on March 6, 1945 As soon as he was hit, he had the strange sensation that the right side of his body was

13 Riddoch, G Phantom Limbs and Body Shape, Brain **64** 197-222, 1941 Schilder, P The Image and the Appearance of the Human Body, Psyche Monographs 4, London, Kegan, Paul, Trench, Trubner & Co, Ltd, 1935

14 The state of being adapted to a continuous stimulus may be terminated by the addition of a new stimulus (which, of necessity, alters the total stimulus configuration) When the patient looked at, moved or touched the affected hand, a change in the stimulus situation was inevitable With this there followed a restoration of the original perceptive state and, consequently, of the body image

spinning, but not the left side A few moments later the right arm and leg twitched and soon felt "dead" Then he found he could not speak, although he knew what he wanted to say He was given emergency treatment and evacuated to a hospital Within two days the paralysis and numbness on the right side began to recede, and speech began to improve A roentgenogram of the skull revealed two lines of fracture involving the left parietal bone

The patient continued to improve and seemed to do well until June 17, when he had a right-sided convulsion This, again, was preceded by a spinning sensation on the right side of the body and face On several occasions he noticed tingling in the right lower part of the leg, but as a rule he had the sensation of "a rubber stocking dressed over this limb" The following week he had another attack, which began with twitching in the right arm This was soon followed by paralysis, and with this he had a sensation of rapid whirling and revolving of the arm, even when the extremity was still Neurologic examination on June 25 disclosed nothing of significance except for residual motor aphasia and some changes in the sensory spheres When he was examined with single stimuli, the sensory status appeared to be normal, but when he was tested with simultaneous bilateral painful stimuli, there was slight dulling on the right side of the body Light rubbing on the lateral side of the right calf yielded a sensation of tingling All other sensations, including those elicited on special visual examinations, were practically normal A pneumoencephalogram at this time revealed moderate dilatation of the ventricular system, especially of the left lateral ventricle

Within the next three weeks the patient had five more seizures on the right side, and, except for a sensation of falling to the right, the whirling and spinning sensations were no longer present

On July 4 an osteoplastic flap was raised for resection of scar tissue and adhesions The left frontoparietal bone near the sagittal suture was found to be soft and the underlying brain tissue degenerated After this, he went home on convalescent leave for thirty-five days, and when he returned he felt somewhat improved His speech was less hesitant, and the peculiar paresthesias in the right leg had disappeared

Special Sensory Examinations (Sept 6, 1945).—1 Pain Sensation Routine examination with single stimuli, such as the prick of a pin, produced sensations which were apparently of equal intensity throughout the body However, with application of graduated stimuli measurement of duration of after-sensation and adaptation time showed a difference There was a distinct abnormality on the right side, especially in the limbs The sensory disturbances about to be described were most profound in the distal portions of the extremities

(*a*) Stimulation on right side A 2 5 Gm weight stimulus with a no 10 needle point applied continuously on the dorsum of the distal phalanx of the right index finger just below the finger nail produced a series of sensations, from that of a point to that of pressure, at the end of 40 seconds This sensation of pressure changed back to sensation of pain within 75 seconds The pain was dull and increased in severity within 110 seconds This sensation fluctuated in intensity and remained throughout the period of application of the stimulus, which was 362 seconds When the stimulus was removed, the patient insisted that the "pin" was still there and that it was painful At this time he also volunteered the information that the "pin" was moved farther down (distally) toward the tip and that he could feel the needle track for about ¼ inch (0 6 cm) The after-sensations (those of a "pin," pain and pressure) were present for over 5 minutes.

(*b*) Stimulation of left side The same type of stimulus applied to the corresponding point on the left side produced a change from sensation of a point to that of pressure within 40 seconds The pressure disappeared entirely at the end of 100 seconds Removal of the stimulus produced a slight pricking sensation, which lasted 5 seconds

(*c*) Bilateral simultaneous stimulation On double simultaneous stimulation of these foci with 2 5 Gm weights, there was a sensation of pain on both sides Sensation on both sides became weak within 25 seconds, that on the left changed to a sensation of pressure within 40 seconds, and became faint and almost disappeared within 105 seconds On the right, the sensation of pain persisted, as well as the sensation of a "pin" However, the sensation of pain on the right fluctuated and changed to a sensation of pressure and of dull pain The latter sensations continued to fluctuate for over 4 minutes When the stimuli were removed, the patient felt the "pin" again on each side, but the sensation on the right was more painful The after-sensation on the right lasted well over 2 minutes, while that on the left was present for 10 seconds Experiments with stimuli of lighter weight, such as the common pin, revealed these changes to an even more striking degree A summary of the observations are recorded in table 2

TABLE 2—*Application of Weight of Common Pin, with Point, Separately on Dorsum of Each Index Finger at Distal Phalanx* *

Right		Left	
Time, Sec	Sensation	Time, Sec	Sensation
1	Pinpoint	1	Pinpoint
20	Pinpoint	10	Pinpoint
30	Pinpoint	14	Fluctuation in sensation
40	Pinpoint and pain	19	Pressure
55	Pressure and pain	29	Less pressure
70	Pressure and pain	45	Pressure sensation almost gone
80	Dull pressure, no pain	55	No sensation
95	Dull pressure, no pain	63	Stimulus removed and sensation of "pin" returned
105	"Pin," pain and pressure	78	After sensation gone
120	"Pin" and pressure		
135	Sensation still there but diminishing		
150	Tingling sensation		
165	Stimulus removed, after sensation of "pin" and tingling continued for the next three minutes, even though patient saw that there was no pain inducing stimulus there, after-sensation fluctuated to a great extent		

* The pin was applied and allowed to rest on the skin, being held in place by a small ring stand The patient felt the prick of the pin as soon as it came in contact with the skin The stimulus was applied first to one hand and after a 5 minute interval, to the other

Simultaneous applications of 5 Gm weights at the base of the great toe yielded sensations which were about equal on the two sides The patient perceived a sharp pain bilaterally, which was most acute on the right side On the right the adaptation time seemed to be prolonged, as was the after-sensation Table 3 is a summary of observations with application of a 2 Gm weight

Simultaneous application of a 2 5 Gm weight stimulus on the right side and of a 5 Gm weight stimulus on the left (each at the base of the great toe) produced a sensation of dulness (no point) on the right and of a sharp point on the left

On removal of the stimulus, at the end of 60 seconds, an after-sensation of a point on the right side was reported, which lasted over 45 seconds There was no after-sensation on the left side Repetition of this experiment later produced pain bilaterally, which lasted only 5 seconds on the right side When a much stronger stimulus (15 Gm) was applied on the left side and 2 5 Gm was applied on the right side, he had no sensation on the right during the simultaneous application of stimuli but experienced a definite after-sensation on the right when both stimuli were removed Thus, the patient showed the phenomena of decreased adaptation time and of cutaneous extinction during bilateral simultaneous but unequal stimulation

Various parts of the body were tested in this manner, but the most profound disorders in after-sensation and adaptation time were present in the right hand and foot, particularly in the distal portions

TABLE 3.—*Application of 2 Gm Weight with No 10 Needle to Base of Fifth Toe, Dorsal Side, Separately on Right and Later on Left Side*

Left		Right	
Time, Sec	Sensation	Time, Sec	Sensation
	"Pin" felt as soon as applied		"Pin" felt as soon as applied
11	Pain getting duller	10	Pinpoint sensation weaker
19	Pinpoint sensation fluctuating	18	"Pin" barely felt
27	Pinpoint sensation weak and almost all gone	29	Pinpoint felt
40	Pinpoint and pressure felt	42	Pressure felt
50	Pinpoint and pressure sensation	50	Faint pressure sensation
60	Patient not certain whether pinpoint is there	60	Patient not sure stimulus is there
72	Stimulus removed but pinpoint still felt	80	No sensation
90	Sensation gradually growing		
100, 120, 150	After sensation weaker during next few minutes, but sensation of point fluctuates		
180	After sensation still present		
210			
235	All after sensation gone		

At the conclusion of all these experiments, the patient volunteered the information that the sensation on the right side seemed more painful and lasted much longer than that on the left side Subsequent repetition of these experiments in the fingers and toes yielded similar results However, the patient observed that although the pain on the right side always lasted longer, it not infrequently seemed duller than, or not so sharp as, that on the left side, also, it was found that at times the pain sensation seemed to disappear earlier than that on the left

At no time was the pain sensation disagreeable, nor did it ever have the characteristics of thalamic pain

2 Temperature Sensation (*a*) When applied separately, a metal object with a temperature of 23 C felt colder in the left hand than in the right hand When the patient held one of these metal objects with each hand simultaneously the sensation of coldness gradually diminished and slowly changed to warmth However, the change in sensation on the right lagged by more than one minute, and as time continued the lag became more pronounced The object in the right hand felt progressively "colder" than that in the left

(*b*) The two hands were then placed in a bowl of water (23 C) The initial sensation in both hands was that of coldness, but in time changes appeared These are summarized in table 4

From these observations it is evident that the adaptation time was much longer on the right side than on the left Because of the gradual and differential nature of the changes the exact duration could not be calculated, but apparently at 68 seconds the left hand began to show a change which was more rapid than that in the right The difference between the two hands was maintained for the next 140 seconds, when adaptation in the right hand caught up with that in the left An after-sensation of coldness was apparent in the right hand, and this lasted well over 4 minutes

(*c*) On holding a cube of ice in each palm, the patient had simultaneous sensations of coldness in the two hands, but that on the left side was more pronounced In 110 seconds burning pain appeared in both hands, but was more intense in the right hand In 170 seconds both hands felt equally cold Of course, there was no manifest adaptation [15] When the ice was removed from the palms

TABLE 4—*Simultaneous Immersion of Both Hands in a Bowl of Water (23 C)*

Time, Sec	Sensations Reported
10	Both hands feel cold
40	No change
55	No change
68	Left hand is getting warmer, right hand remains colder
95	Left hand feels warmer than right
115	Definite difference in temperature sense, right hand feels colder than left
160	Difference is still present (temperature of water is now 25 C)
180	Difference is beginning to be less apparent
210	Hands feel of equal warmth
250	No difference in temperature sensation
280	Right hand feels colder than left
315	Right hand feels colder than left and has a "sensation of numbness," or "dead feeling"
410	Right hand still feels colder than left, cutaneous temperatures as measured with dermotherm are equal on the two sides
480	Difference is still present, but now it is not apparent unless patient "concentrates" on it
500	Difference on right persists, but it is less pronounced

at 200 seconds after-sensations of coldness mixed with burning and dull pain were present in both These after-sensations, which fluctuated in intensity, were of long duration However, the after-sensations on the right were more prolonged and more vivid than those on the left The patient exclaimed that he had the sensation of still holding the ice in the right hand, and he could even sense the weight and the wetness In the left hand he felt a burning pain

3 Tactile Sensation This modality showed the same characteristics as those which were found for pain The adaptation time was often prolonged, and the duration of after-sensation extended from 1 to 3 minutes in the right hand and foot

The disturbances were most pronounced in the acral portions of the extremities on the right side Simultaneous application of a hair analogous to von Frey's

15 Adaptation has certain limits In the normal person, if the hand is held in water which is only a few degrees above or below the temperature of the skin, the sensations of warmth or cold diminish and disappear within a short time However, if the hand is held in water as low as 10 C, the sensation of cold persists for a long time, and there seems to be no manifest adaptation With higher temperatures, above 45 C, there is virtually no adaptation, because of injury to tissue

hairs on each side at corresponding foci produced a sensation of touch bilaterally, but more acute on the right Adaptation was much quicker on the left A prolonged after-sensation was found on the right but not on the left

Simultaneous application of a strong tactile or painful stimulus on the left and a tactile stimulus to the corresponding focus on the right side produced no sensation on the right side, but only on the left Thus, the patient manifested the phenomenon of cutaneous extinction during double simultaneous, but unequal, stimulation However, on the removal of both stimuli there occurred an after-sensation on the right, which seemed to be more apparent and longer in duration than the one on the left

4 Other Perceptions (*a*) Vibration sense was about equal on the two sides He felt the vibrations in the right finger for 30 seconds (the examiner felt the same vibration for 35 seconds) and in the left finger for 37 seconds (examiner felt the same vibration for 34 seconds) In the great toe, vibration was felt for 15 seconds on the right and for 19 seconds on the left On the removal of the tuning fork, the patient had a prolonged after-sensation of touch but not of vibration in the tested areas of the right extremities There was no noticeable after-sensation on the left, at least it did not last long

(*b*) Appreciation of passive movement and ability to recognize position of the digit or toe in space were normal in all respects

(*c*) Two point discrimination was excellently performed on the two sides He could differentiate two points when 3 mm apart (on the right side as well as on the left) Here, again, he complained of an after-sensation of a point on the right side when the compass was removed

(*d*) Point localization was normal He could localize correctly every stimulus applied to different parts of his body

(*e*) Stereognosis was intact He could recognize various objects placed either in his right or in his left hand He was able to describe texture, shape, size and other sensations evoked by the tested object Of course, when he held identical objects between the first two fingers of each hand for a long period without moving his digits or hands, the factors of adaptation became apparent, thus leading to a difference between the two sides The impression of the object on the right became duller and seemed to become adapted more quickly than that on the left

(*f*) Barognosis was normal He could recognize small differences in weights and compare them with either or both hands During these tests it was noted, however, that the patient had a prolonged after-sensation of a weight in the right hand A 480 Gm weight held for 3 minutes with the left hand produced an after-sensation of weight for 10 seconds, whereas the same test with the right hand left an after-sensation for 2 minutes Equal weights placed simultaneously in the two hands for 3 minutes produced a sensation of heaviness in the right hand throughout and after the test The after-sensation in the right hand lasted over 3 minutes Beyond this period there seemed to be a fluctuation of sensation, during which the patient reported an alternating "heaviness" and "lightness" in the hand

(*g*) Graphesthesia was normal with single or double simultaneous stimulation The figure writing, however, produced a noticeable after-sensation in the extremities on the right side

Comment.—The outstanding features in this case are (*a*) prolongation of after-sensations, (*b*) delay in sensory adaptation, and (*c*) appearance of a dull ache during the application of continuous stimulus, pain or

pressure The last symptom (*c*) might have been responsible for the apparent prolongation of the adaptation time for pain sensation The dull ache and the occasional burning and tingling which appeared on continuous stimulation were somewhat similar to the hyperpathia which is found with lesions of the thalamus However, there were no other clinical signs of such involvement Interestingly enough, with double simultaneous and equal stimulation the sensation in the affected limbs seemed to him to be keener than that felt on single stimulation This enhancement of a sensation with paired stimulation seems to be the converse of the phenomenon of extinction, which could be elicited in some cases under the same conditions In fact, in this patient the simultaneous application of a strong stimulus on the normal side and a weak stimulus on the affected side produced a reduction in sensitivity, and even a reduction in sensory adaptation time, in the affected limb Thus, this patient showed both phenomena, namely, (*a*) enhancement of a sensation with apparent prolongation of the adaptation period and (*b*) reduction of the adaptation period with ultimate extinction of sensation It is not improbable that these phenomena are related and appear to be the positive and the negative phase of the various sensory mechanisms which are operative in this patient Analogous to these positive and negative phases of a given sensory mechanism are the facilitation and suppression (or extinction) phenomena for motor function, as demonstrated by Dusser de Barenne and his collaborators [16] They found that by changing the strength, frequency, duration, character and timing of stimuli, either facilitation or extinction could be obtained on exciting a given focus in the motor cortex of the chimpanzee or monkey Similar positive ("firing") and negative ("suppression") changes were found on stimulating the sensory cortex [17] These experimental data may conceivably explain the clinical observation made in patients with injuries of the parietal lobe, the stimuli in these cases arising, of course, from cutaneous zones

16 (*a*) Dusser de Barenne, J G Simultaneous Facilitation and Extinction of Motor Response to Stimulation of a Single Cortical Focus, Am J Physiol **116** 39-40, 1936 (*b*) McCulloch, W S On the Nature and Distribution of Factors for Facilitation and Extinction in the Central Nervous System, ibid **119** 363-364, 1937 (*c*) Dusser de Barenne, J G, and McCulloch, W S Factors for Facilitation and Extinction in the Central Nervous System, J Neurophysiol **2** 319-355, 1939 (*d*) Dusser de Barenne, J G, Garol, H W, and McCulloch, W S The Motor Cortex of the Chimpanzee, ibid **4** 287-303, 1941

17 Dusser de Barenne, J G, and McCulloch, W S Functional Organization in the Sensory Cortex of the Monkey (Macaca Mulatta), J Neurophysiol **1** 69-85, 1938 Dusser de Barenne, J G, Garol, H W, and McCulloch, W S Functional Organization of Sensory and Adjacent Cortex of the Monkey, ibid **4** 324-330, 1941

Another feature which this, and the first, case illustrates is that a stimulus applied on one side of the body alters the sensation obtained on the opposite side or in other parts of the body [18] All these observations support the experimental observations of Dusser de Barenne, who concluded that sensory function is bilaterally represented [19] One sensory cortex receives impulses from both sides of the body, conversely, a sensation on one side of the body is represented in both sensory cortices

GENERAL COMMENT

It is well known that many forms of sensation are adaptable Adaptation for pressure has been recognized for years For example, a glove on the hand, a ring on the finger or hat on the head become unfelt after a short interval Adaptation for thermal, olfactory and gustatory sensations has been described [20]

Adaptation for pain has also been recognized, and, notwithstanding doubts expressed by Boring,[20b] Strauss and Uhlmann [21] (1919) and, later, Burns and Dallenbach (1933)[22] found that pain is adaptable The adaptation times, however, vary considerably with the subject and with the spot stimulated There are individual differences and wide fluctuations The period of adaptation is not greatly influenced by the intensity of the stimulus, by fatigue or by ennui Slight movements of the stimulus or of the tissue beneath the stimulus do not interfere with the phenomenon of adaptation All that seems to be required to obtain the phenomenon is a stimulus of unvarying intensity The pain aroused by a punctiform stimulus is replaced by a sensation

18 There are instances in which a stimulus applied to an anesthetic side of the body elicits a sensation on the opposite (normal) side (Ray, B S, and Wolff, H G Studies on Pain "Spread of Pain", Evidence on Site of Spread Within the Neuraxis of Effects of Painful Stimulation, Arch Neurol & Psychiat **53** 257-261 [April] 1945) This has been found in patients with a lesion of the spinal cord produced by ventrolateral chordotomy Ray and Wolff explained the perception of pain on the normal side when a strong noxious stimulus is applied to the analgesic area on the basis of spread of excitation via internuncial neurons in the spinal cord This "postulated spread of excitatory processes associated with pain of high intensity primarily involves the segmented structures, although secondarily the suprasegmental structures are implicated in perception, localization and reaction"

19 Dusser de Barenne, J G Central Levels of Sensory Integration, A Research Nerv & Ment Dis, Proc **15** 274-278, 1935

20 (*a*) Woodworth, R S Experimental Psychology, New York, Henry Holt & Company, Inc, 1938 (*b*) Boring, E Sensation and Perception in the History of Experimental Psychology, New York, D Appleton-Century Company, Inc, 1942

21 Strauss, H H, and Uhlmann, R F Adaptation to Superficial Pain, Am J Psychol **30** 422-424, 1919

22 Burns, M, and Dallenbach, K M The Adaptation of Cutaneous Pain, Am J Psychol **45** 111-117, 1933

of pressure before adaptation takes place Thus, there is a gradual subsidence from maximal pain, evoked by a given stimulus (2 5 to 7 5 Gm), through a sensation of pressure to total indifference The sequence of experiences reported by a subject who has a 2 5 to 7 5 Gm weight stimulus with a no 10 needle point applied to the forearm is as follows sharp, intense pain, sharp pain, pain, dull pain, weak pain, pressure, weak pressure, tickle, no sensation The adaptation time varies in different parts of the body, but it seems to be approximately equal for corresponding points on the two sides [23] On removal of the stimulus, there is usually an after-sensation

Thus, in the normal subject, if it takes 80 seconds for sensation produced by a 2 5 Gm weight point stimulus to disappear on the right index finger, it might take 70 to 90 seconds on the left index finger However, if the total adaptation time is 10 or 15 seconds on one side and 70 to 90 seconds on the other, the difference becomes significant It is noteworthy that the reduction in the entire adaptation period is not always proportional for each of the intrinsic changes in sensation experienced in various pathologic conditions For instance, in a defective sensory area due to a cerebral lesion the total adaptation time for a 5 Gm stimulus may be 15 seconds Here, the sensation of pain may change to one of pressure at the end of 10 seconds, there remaining a sensation of pressure for 5 seconds On the other hand, the adaptation time in a sensory area affected by a lesion of a peripheral nerve may be 50 seconds, and here the sensation of pain might disappear in 10 or 15 seconds, leaving a sensation of pressure for 40 or 35 seconds

In summary, sensory adaptation in cases of cerebral lesions is represented by changes from pain to pressure which take place much more rapidly than in cases of lesions of the peripheral nerves The total time required for adaptation is usually shorter in cases of lesions of the parietal lobe than in cases of lesions of peripheral nerves As a rule, the sensation of pressure, which follows the initial sensation of pain, during adaptation, is of longer duration with peripheral than with central lesions Adaptation for such perceptual performances as stereognosis, barognosis and kinesthesia, with resultant alteration in the body image, probably exists in the normal person, but few, if any, studies of such a phenomenon have been made by the neurologist or the psychologist The first case here presented demonstrates the presence of such a mechanism for some of these perceptions The disappearance of a complex perception, such as the position or presence of a limb in space or the ability to sense a weight during a prolonged act, would seem to point to "adaptation" on a central or cortical

23 Some of the studies on pain adaptation in the normal subject in this series have been made by Lieut Comdr L D Boshes (MC), U S N R

level, despite the fact that the primary modalities are also affected in these tests Certainly, "adaptation" for barognosis and other complex cutaneous perceptions must ultimately occur in the parietal cortex Thus, lesions in the cortex may lead to a reduction in the sensory adaptation time Interference with sensory conduction in the periphery may also decrease the time, but not nearly as much as that caused by a cortical lesion It is not unlikely that central adaptation occurs also in visual perception [24] and should be apparent under pathologic conditions As a matter of fact, in a series of patients with visual disturbances produced by gunshot wounds implicating the optic pathways, certain observations seem to indicate that the mechanism for central adaptation may be operating for visual perception Thus, in a case of a gunshot wound through the midparieto-occipital area, the patient found that if he fixed on a point for a few seconds three quarters of the entire field of vision "faded out" Perimetric examination revealed apparently intact fields for perception of motion, but transient defects for color, in these three quadrants Since in this patient no visual stimuli were added to his field of vision and since fixation was steady, it would be difficult to explain the "fading out" of his perception in terms of the phenomenon of visual extinction alone [25] A possible interpretation is that the vision "faded out" on the basis of central adaptation

Although most patients with injuries to the parietal lobe show a decrease in the period of adaptation, there are some instances, such as case 2, in which the period is prolonged This prolongation may be only apparent, since it seems to be associated with a fluctuating dull, sometimes tingling, pain, which has been found to occur late in the period of continuous application of a stimulus This dull pain may thus interfere with the patient's ability to adapt to pain, temperature and pressure sensations Yet it is uncertain which comes first—whether the appearance of pain prevents completion of adaptation or prolongation of the adaptation causes the appearance of pain Since there is no initial alteration of the threshold and no hyperpathia in these cases, it would seem that the latent dull pain is due to lack of adaptation, and perhaps a resultant summation A possibility which must be considered is that a stimulus in the parietal cortex

24 In point of fact, peripheral mechanisms of adaptation in vision (dark and light adaptation) have been thoroughly studied by physiologists and psychologists

25 It should be recalled that extinction of visual perception (as well as cutaneous perception) occurs on double simultaneous stimulation The patient can perceive a stimulus placed in the affected field of vision, but as soon as another stimulus is placed in the normal field perception in the affected field becomes extinct He cannot perceive simultaneously objects placed in the normal and in the involved area

may "fire" neurons in the thalamus and thus indirectly produce thalamic pain [26] Whatever the explanation may be, it is a fact that in a patient with injury to the anterior parietal lobe the sensory adaptation period seems to be prolonged

Concomitant with a pathologic increase in adaptation time is a prolongation of the after-sensation Painful, thermal or tactile sensations may persist after the removal of the respective stimulus or, having been lost under adaptation, may recur on the withdrawal of the stimulus [27] In most cases of injury to the parietal lobe, in which, as has been seen, adaptation time is reduced, the duration of the after-sensation is likewise reduced or abolished The same is true in cases of injury to peripheral nerves Conversely, prolongation of after-sensation is found but uncommonly in cases of damage to the parietal lobe In cases of injury to peripheral nerves the after-sensation is not infrequently prolonged, especially in the hyperesthetic cutaneous area

This prolongation of cutaneous after-sensation [28] is also difficult to explain In the normal subject after-sensations may show instability and variability, which are dependent on central factors According to Holland,[29] it makes a great difference whether the subject is passive or whether he assumes an active attitude, in which he attempts to secure as much cutaneous experience as possible For a given stimulus during a passive attitude, the after-sensation lasted from 0 7 to 2 0 seconds, and the secondary after-sensations were few and brief During an active attitude, the primary after-sensations lasted an average of 4 seconds (although sometimes as long as 200 seconds), and the secondary after-sensations were numerous and often of long duration Although an active attitude may thus produce persistence of an after-sensation in the normal subject, it could not explain the phenomenon in case 2, in which after-sensations were prolonged on the affected side, particularly in the distal portions of the extremities One must assume that the persistence of the after-sensation was due to centrally excited sensations as result of a lesion in the anterior parietal lobe

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26 Dusser de Barenne, J G Sensorimotor Cortex and Thalamus Opticus, Am J Physiol **119**·263, 1937 Dusser de Barenne, J G, and McCulloch, W S The Direct Functional Interrelation of Sensory Cortex and Optic Thalamus, J Neurophysiol **1**·176-186, 1938

27 The experimental psychologist divides after-sensations into two phases persistence, or primary after-sensation, and recurrence, or secondary after-sensation [20b]

28 An analogous situation may be found in visual after-imagery In a patient with a lesion of the visual pathways and cortex there was marked prolongation in the duration of the visual after-image

29 Holland, R T On the After-Sensation of Pressure, J Exper Psychol **3** 302-318, 1920

These observations suggest that perception is greatly influenced by the mechanisms of sensory adaptation and after-sensation, which are partly of central origin With disease these mechanisms become apparent, sometimes to such an extent that they produce manifest symptoms

Whether adaptation taken in a clinical sense (as used in this paper) is directly related to the phenomena of adaptation in the psychologic sense (as measured at the peripheral level) is difficult to say It is tempting to draw an analogy between the clinical adaptation phenomenon for perceptions and the phenomenon of adaptation of sensory function as described by physiologists, such as that for single optic nerve fibers, described by Hartline [30] and others At least it is reasonable to assume that these characteristics of function (changes in adaptation) at the peripheral end organ and neuron are reflected in the more complex functions of the cerebral cortex It may also be argued that central adaptation is the result of cumulative effects of adaptation in single neuronal units (in the physiologic sense) But in view of the paucity of available data at this time such deductions are still in the speculative stage

SUMMARY

A patient with a gunshot wound of the left posterior parietal and occipital lobes showed disturbances in visual, cutaneous and proprioceptive senses on the right side of his body These defects were elicited under special conditions Whereas with single stimulation his vision appeared to be intact, simultaneous stimulation of his right and left fields of vision caused the image on his right to become extinct This phenomenon of extinction was found in various forms, from fluctuation and blurring to complete invisibility of an image A similar phenomenon was found for cutaneous perception Besides this, the patient showed a reduction in the adaptation time for cutaneous and proprioceptive modalities The latter was pronounced enough to produce a disorder in his body image

Another patient, with a gunshot wound in the left anterior parietal and posterior frontal lobes, showed motor and sensory disturbances in the right side of his body The sensory changes could be elicited only under special conditions and were expressed as a prolongation of the periods of sensory adaptation and after-sensation With paired equal stimulation, sensation was apparently enhanced on the affected side With paired simultaneous stimulation in which a strong stimulus was applied to the left side and a weak stimulus to the right side,

30 Hartline, H Response of Single Optic Nerve Fibers of Vertebrate Eye to Illumination of Retina, Am J Physiol **121** 400-415 (Feb) 1938

there was reduction of sensory adaptation time, and even extinction of sensation This case thus illustrates the phenomena of "enhancement and extinction" of sensation, either of which could be obtained on stimulating the same area of the skin at different times and under different conditions It is analogous to the experimental observations made by Dusser de Barenne and associates [16d] for motor function in the chimpanzee These patients also showed decrease or increase in after-sensations

These observations reveal that most of the disturbances in these patients were due to normal mechanisms (such as rivalry with resultant dominance, sensory adaptation and after-sensations) which became apparent under pathologic conditions, such as lesions in the parietal lobe Why these mechanisms become so apparent is not clear Without the foregoing considerations and special investigations of sensations, most of the symptoms could not be explained, because routine neurologic examination for sensation revealed an essentially normal status in both these patients

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SIGNIFICANCE OF CORNEAL AND PHARYNGEAL REFLEXES IN NEUROLOGY AND PSYCHIATRY

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DURING the course of the neurologic examination, deviations from classic normality occur even in the absence of organic disease of the nervous system Much experience and intuition are required to distinguish normal variations from pathologic signs, and too frequently the presence of asymmetry is allowed to constitute the determining factor It would seem only reasonable to assume that some of the determinants of these deviant, but nonpathologic signs might have significance for the clinician For example, variations in reflex responses might be found to occur in definite patterns, so that a single observation could be interpreted in terms of its conformity to the pattern set by the other reflexes rather than in terms of an absolute standard Another possibility is that psychic attitude might be expressed by, or might determine, patterns of reflex variability Accordingly, complete neurologic examinations were performed and the results recorded in conjunction with diagnostic psychiatric interviews for a series of patients, and relationships are being sought in this codified material In this paper the distribution of variations in corneal and pharyngeal reflexes and their relations to other physical and to mental signs are presented

It is current medical belief, expressed less frequently in psychiatric textbooks than in others, that hysterical conversion symptoms are often accompanied by absence of corneal and pharyngeal reflexes Monrad-Krohn[1] stated that "the pharyngeal reflex may be absent in hysteria," thus implying that in the absence of hysteria (and of organic disease of the brain) this reflex is always present Moreover, he went on to say that, although the "conjunctival reflex is often absent in normal individuals, the corneal reflex is a constant phenomenon, the absence of which has pathologic significance" Wechsler[2] and Brain,[3] on the

From the Medical Center for Federal Prisoners, Springfield, Mo, and St Elizabeths Hospital, Washington, D C

1 Monrad-Krohn, G H Clinical Examination of the Nervous System, ed 7, New York, Paul B Hoeber, Inc, 1941

other hand, unequivocally stated that the corneal, as well as the pharyngeal, response may be absent in hysteria In view of this popularly established belief, the results of actual analysis have proved surprising

MATERIALS AND METHOD

One hundred and forty-one patients were included in this study Of these, 58 were taken from the wartime population of St Elizabeths Hospital, and the group consisted primarily of young Navy men in the various stages of their acute psychoses, the remaining 83, a group composed for the most part of young criminal psychopaths and maladjusted persons, whose mental state falls frequently just within the limits of psychiatric normalcy, were examined at the Medical Center for Federal Prisoners Of the entire group, the diagnosis of encephalopathy was made for 30 patients The degree of involvement was usually mild or moderate, and the chief etiologic factors were syphilis of the central nervous system, arteriosclerosis, alcoholism and trauma These 30 patients are referred to later as the "organic group," which by our definition excludes 8 patients who exhibited convulsive seizures but no neurologic abnormality other than a dysrhythmic electroencephalogram

It is thought advisable to describe in some detail the technics employed for the elicitation of the various reflexes studied Reflex response to tactile stimulation of the cornea was tested in the following manner A small wisp of sterilized absorbent cotton was drawn out and twisted to form a thick and slightly tapering thread at least 1 inch (2 54 cm) long Care was exercised to see that the thread terminated abruptly at the stimulating end The patient was instructed to look upward and to the right The cotton thread was then slowly advanced close to, and parallel with, the surface of the face and the conjunctiva of the left eye from left to to right until its free end rested securely on the left cornea, infralateral to the pupil and at a point about 2 mm inside the sclerocorneal junction (limbus corneae) Thus, the cotton stimulator and the moving hand of the examiner were at all times outside the patient's field of vision An analogous procedure was performed on the right cornea Responses were graded on the basis of promptness and forcefulness into five categories normal, slightly, moderately and greatly diminished, and absent The chief purpose of such fine grouping was to insure careful observation For statistical analysis, however, the first three categories were combined to form the positive corneal (C+) group, and the last two, to constitute the negative corneal (C—) group

The following procedure was used to test the pharyngeal reflex The patient was approached with a flashlight and a tongue depressor He was instructed to open his mouth, and as the tongue depressor was advanced he was requested to say "Ah," just as though an ordinary inspection of the pharynx were proceeding The stick was gently passed backward under plain view until it rested securely against the posterior pharyngeal wall in the midline Responses varied from prompt and forceful gagging and coughing movements to none at all Intermediate responses consisted of orderly contractions of the faucial musculature As with the corneal reflexes, responses were classified under five groups, from which two

2 Wechsler, I S Textbook of Clinical Neurology, ed 4, Philadelphia, W B Saunders Company, 1939

3 Brain, W R Diseases of the Nervous System, ed 2, London, Oxford University Press, 1940

compound categories, positive pharyngeal (P+) and negative pharyngeal (P—) reflexes, were formed for purposes of statistical comparison

Other examinations and tests, including the Mayer test and tests for the abdominal (skin), deep and Hoffmann reflexes, were executed by standard manipulations, and conventional criteria were followed [4]

RESULTS

1 *Distribution of Reflex Responses in Entire Series*—It will be observed (table 1) that over one third of all the patients in this series exhibited a marked diminution or entire absence of the corneal reflex (C—), and that this proportion is scarcely decreased when the patients with organic disease are removed from the series Of the latter group, more than half showed absence of the corneal reflex (In only 1 patient was there any significant difference between the responses on the two sides) With respect to the pharyngeal reflexes, more than two thirds of the entire series fell in the negative group, and when the patients with organic disease are excluded, almost three quarters of the patients showed the marked diminution or absence of response Moreover, a positive pharyngeal reflex was twice as frequent among the patients with organic disease as among the others, and this difference is significant at the 1 6 per cent level (odds, 60 1)

The results obtained by combining the corneal and the pharyngeal categories to form four groups (C+ P+, C+ P—, C— P+ and C— P—) are also included in table 1 It appears, first, that there is no significant correlation between the corneal and the pharyngeal responses in patients either of the nonorganic or of the organic group Second, the distributions for the total series and for the patients without organic disease are remarkable in that in each series almost half the patients fall into the C+ P— group, about one-quarter each in the C+ P+ and in the C— P— group, and the small remainder in the C— P+ group This must not be interpreted as indicating that there is any physiologic antagonism between a negative corneal reflex and a positive pharyngeal reflex, for when the incidence of negative corneal reflexes (C—), 36 per cent, is multiplied by the incidence of positive pharyngeal reflexes (P+), 31 per cent, in the total series, the product is 10 per cent, which is approximately the observed incidence for the C— P+ group Among the patients with organic disease, however, the results are different It will be recalled that here one-half the patients exhibited a positive corneal reflex and one-half exhibited a positive pharyngeal reflex Assuming that the independence of corneal and pharyngeal responses holds even among the patients with organic disease, one may expect that about

4 Monrad-Krohn [1] Wechsler [2] Brain [3]

TABLE 1—*Distribution of Patients According to Corneal and Pharyngeal Responses*

	1 Sum or Mean	2 C+	3 C—	4 P+	5 P—	6 C+ P+	7 C+ P—	8 C— P+	9 C— P—
A Total series	111	90	51	44	97	31	59	13	38
B Percentage of total series	100	64	36	31	69	22	42	9	27
C Patients without organic disease	111	76	35	29	82	23	53	6	29
D Percentage of patients without organic disease	100	68	32	26	74	21	48	5	26
E Patients with organic disease	30	14	16	15	15	8	6	7	9
F Percentage of patients with organic disease	100	47	53	50	50	27	20	23	30
G Percentage of patients with organic disease in total series	21	16	31	34	15	26	10	54	24

one quarter of the patients will fall into each of the four groups, and they do This difference between the distribution of the patients with organic disease and that of the total population among the various CP groups is so great that the odds are much less than 1 1,000 that any randomly selected group similarly analyzed would differ more from our total series ($X^2 = 34.75$)

Another way of presenting the same results is to compute the proportion of patients with organic disease within any of the established categories Thus, as expected, while only 16 per cent of the patients with positive corneal responses belong to the organic group, 31 per cent of the patients with negative corneal responses belong to that group, whereas 15 per cent of the patients with negative pharyngeal responses and 34 per cent of those with positive pharyngeal responses belong to the organic group In the compound categories, only about 1 of 10 patients in the C + P — category had organic disease of the brain, but more than half the patients in the C — P + classification were considered to have organic disease, and this difference is statistically significant (C R = 3)

From these results, it is believed one is justified in stating that any patient who exhibits absence of corneal reflexes in the presence of an active pharyngeal reflex should be strongly suspected of having organic disease of the brain

2 *Distribution of Reflex Responses According to Diagnostic Groups* —For the 141 patients in our series, 184 diagnoses were made, the distribution of those diagnoses according to reflex responses is shown in table 2 The percentages given in lines D, H and J were constructed by dividing the number of diagnoses for the groups with schizophrenia, psychopathic personality and organic disease of the brain, respectively, by the number of patients in the column Thus, the entry 39 per cent in line D, column 2, signifies that 39 per cent of the patients in the group with positive corneal responses (C +) bore the diagnosis of schizophrenia Except in the group with organic disease, which has previously been discussed, dramatic differences do not appear The differences between the incidence of psychopathic personality in the groups with positive and negative corneal reflexes (C + and C —), on the one hand, and the incidence of schizophrenia in the groups with positive and negative pharyngeal reflexes (P + and P —), on the other, are less than 1 5 times their respective standard deviations, and do not even reach the 10 per cent level of significance

However of the 56 schizophrenic patients, 17 had at the time of examination recovered practically completely, 10 were slightly ill, 18 were moderately so and only 11 were considered seriously ill By assigning values of 0, 100, 200 and 300 to these four groups, respec-

TABLE 2—*Distribution of Patients According to Diagnosis and Corneal and Pharyngeal Responses*

		1 Total	2 C+	3 C—	4 P+	5 P—	6 C+ P+	7 C+ P—	8 C— P+	9 C— P—
A	Total number of patients	141	90	51	44	97	31	59	13	38
B	Total number of diagnoses	184	118	66	60	124	42	76	18	48
C	Number of schizophrenic patients	56	35	21	14	42	11	24	3	18
D	Percentage of schizophrenic patients (C/A)	40	39	41	32	43	35	41	23	47
E	Index of illness* among schizophrenic patients	141	160	110	107	152	118	179	67	117
F	Amount of schizophrenic activity* for group (D×E=C×E/A)	56	63	45	34	65	41	73	15	55
G	Number of patients with psychopathic personality	49	35	14	15	34	11	24	4	10
H	Percentage of psychopathic patients (G/A)	35	39	27	34	35	35	41	31	26
I	Number of patients with organic disease of brain	30	14	16	15	15	8	6	7	9
J	Percentage of patients with organic disease of brain (I/A)	21	16	31	34	15	26	10	54	24
K	Number of patients with simple adult maladjustment	17	11	6	8	9	6	5	2	4
L	Number of mentally defective persons	10	9	1	4	6	3	6	1	
M	Number of epileptic patients †	8	7	1	2	6	2	5		1
N	Number of psychoneurotic patients	6	4	2		6		4		2
O	Number of patients with manic depressive psychosis	5	1	4	1	4		1	1	3
P	Miscellaneous groups	3	2	1	1	2	1	1		1

* The indexes in line E were computed by averaging assigned values of 0, 100, 200 and 300 for recovered and slightly, moderately and very ill schizophrenic patients, respectively The figures in the following line, F, were obtained by multiplying the appropriate figures in lines D and E, so that the products measured the net amounts of schizophrenic activity for the respective groups

† Includes patients exhibiting seizures without clinical evidence of encephalopathy

tively, index numbers were obtained which vary among the several CP categories, as indicated on line E of table 2 For example, 160 (line E, column 2) indicates that the severity of the psychotic process among the schizophrenic patients with positive corneal reflexes was on the average between slight and moderate Now, by multiplying this average degree of activity among the schizophrenic patients by the percentage incidence of schizophrenia, one obtains an index which can be said to measure the average schizophrenic activity for the column (line F) Thus, the average schizophrenic activity among the patients with negative pharyngeal reflexes is 65, and that among the patients with positive pharyngeal reflexes, 34, with a difference of 31, which is significant to the 5 per cent level (C R = 1 91) The analogous computation for positive and negative corneal reflexes yields a difference of 18, which is not significant

It appears from the foregoing analysis that the schizophrenic process may be associated with obtundation of the pharyngeal reflex

3 *Relation of the Corneal and Pharyngeal Reflexes to the Abdominal Reflex*—In table 3 the results of examination of the abdominal reflexes are summarized Three groups of patients are considered those with normal abdominal reflexes, those with overactive reflexes and those with underactive reflexes, the last group including patients with absence of reflexes In addition, index numbers for average activity of the abdominal reflex were computed by assigning a value of 0 to patients with normal reflexes, 100 to patients with overactive reflexes, —100 to patients with underactive reflexes and —200 to patients with absence of reflexes (When the abdominal reflexes were asymmetric, the patient was classified with respect to the more abnormal reflex) In lines D and K, these index numbers are listed for the corneal and pharyngeal categories The contrast between the mean index for patients with organic disease (—74) and the mean index for patients with nonorganic disease (—3) is striking and is certainly consistent with the well established underactivity of the abdominal reflexes in patients with organic disease of the brain

Closer examination of line D reveals that division of the patients into categories of positive and negative corneal reflexes (C + and C —) yields groups whose average abdominal reflex activity does not differ from the normal However, a similar classification in terms of positive and negative pharyngeal reflexes results in a significant difference (C R = 4), patients with an active pharyngeal reflex exhibit, on the average, a slightly overactive abdominal response, while patients with an inactive pharyngeal reflex tend to exhibit a slightly underactive abdominal reflex According to some opinions expressed in the litera-

TABLE 3—*Distribution of Patients According to Abdominal Reflex Activity and Corneal and Pharyngeal Responses*

		1	2	3	4	5	6	7	8	9
		Sum or Mean	C+	C—	P+	P—	C+ P+	C+ P—	C— P+	C— P—
A	Total number of patients	86	59	27	31	55	22	37	9	18
B	Total number of patients without organic disease	59	46	13	17	42	15	31	2	11
C	Total number of patients with organic disease	27	13	14	14	13	7	6	7	7
D	Index number for patients without organic disease *	—3	—2	—8	29	—17	27	—16	50	—18
E	Number with normal abdominal reflexes	19	17	2	7	12	6	11	1	1
F	Percentage with normal abdominal reflexes (E/B)	32	37	15	41	29	40	36	50	9
G	Number with overactive abdominal reflexes	20	15	5	8	12	7	8	1	4
H	Percentage with overactive abdominal reflexes (G/B)	34	33	38	47	29	47	26	50	36
I	Number with underactive abdominal reflexes †	20	14	6	2	18	2	12		6
J	Percentage with underactive abdominal reflexes (I/B)	34	30	46	12	43	13	39		55
K	Index number for patients with organic disease *	—74	—92	—57	—93	—54	—128	—50	—57	—57
L	Number with normal abdominal reflexes	5	3	2	2	3	1	2	1	1
M	Number with overactive abdominal reflexes	3	1	2	1	2		1	1	1
N	Number with underactive abdominal reflexes †	19	9	10	11	8	6	3	3	5
O	Percentage of patients with organic disease among those with overactive abdominal reflexes (M/G+M)	13	6	29	11	14		11	50	20
P	Percentage of patients with organic disease among those with normal abdominal reflexes (L/E+L)	21	15	50	22	20	14	15	50	50
Q	Percentage of patients with organic disease among those with underactive abdominal reflexes (N/I+N)	49	39	63	85	31	75	20	100	46
R	Percentage of patients with organic disease among total number of patients (C/A)	31	22	52	45	24	32	16	78	39

* Computed by assigning values of 100 to patients with overactive abdominal reflexes 0 to patients with normally active abdominal reflexes, —100 to patients with underactive abdominal reflexes, and —200 to patients with absence of abdominal reflexes When unequal abdominal responses were elicited, the patient was categorized according to the more abnormal response

† Patients with absence of abdominal reflexes included in this group

ture (cited by Wartenberg [5]), overactivity of the abdominal reflex is attributed to cortical irritation, just as absence is attributed to a destructive lesion of the pyramidal tract However, Monrad-Krohn (cited by Brock [6]) suggested that activity of the abdominal reflex is increased by a destructive lesion of the red nucleus, i e, exaggeration and diminution of the reflex are the results of two entirely different mechanisms Further examination of table 3 will show that among our patients without organic disease of the brain 47 per cent of those with an active pharyngeal reflex had an overactive abdominal response, whereas 29 per cent of the patients with an inactive pharyngeal reflex showed an overactive abdominal reflex Moreover, the corresponding proportions for patients with an underactive abdominal reflex are 12 and 43 per cent In short, an overactive abdominal reflex is associated with an active pharyngeal reflex and an underactive abdominal reflex with an inactive pharyngeal reflex, no trace of a dual mechanism appears among these patients

Reference to column 1, lines O, P and Q, indicates that of the patients with an overactive abdominal reflex, 13 per cent had organic disease of the brain, of those with a normal abdominal reflex, 21 per cent had organic disease of the brain, and of the patients with an underactive abdominal reflex, 49 per cent had organic disease of the brain These results are entirely consistent with the usual clinical interpretation of absence of the abdominal reflex From the data given in the foregoing paragraph, one may anticipate a useful and, to our knowledge, hitherto undescribed relationship If among patients without organic disease of the brain the activity of the pharyngeal and that of the abdominal reflex are closely associated, then the presence of an underactive abdominal reflex or its absence should be a much more reliable indicator of organic disease in the presence of an active pharyngeal reflex than in the presence of an inactive one In the latter case even patients without organic disease of the brain may be expected to show underactivity of the abdominal reflex Reference to columns 4 and 5, lines O, P and Q, confirms this a priori conclusion Thus, among patients with a normal or with an overactive abdominal reflex, the presence or absence of the pharyngeal reflex does not influence the percentage incidence of organic disease of the brain However, among patients with an underactive abdominal reflex, 85 per cent of those who simultaneously exhibit an active pharyngeal reflex have organic cerebral disease, of those with an inactive pharyngeal reflex, only 31 per cent

5 Wartenberg, R Studies in Reflexes I History, Physiology, Synthesis and Nomenclature, Arch Neurol & Psychiat **51** 113 (Feb) 1944

6 Brock, S Anatomical and Physiological Basis of Neurology, Baltimore, William Wood & Company, 1933

have organic disease of the brain In this series of patients an underactive abdominal reflex was almost three times as significant of organic disease in the presence of pharyngeal activity as in its absence

One now has two sets of reflex combinations, each of which is a better indicator of the presence of organic disease of the brain than any of its component reflexes taken individually first, the combination of active pharyngeal and inactive corneal reflexes, and, second, the combination of active pharyngeal and underactive abdominal reflexes Although superficially these combinations might seem to be analogous, really they achieve their significance by quite different mechanisms In the first, in the group with inactive corneal reflex (C —), organic disease is 31/21 times as frequent as in the total population, and in the group with active pharyngeal reflex (P +) it is 34/21 times as frequent If there is no association between corneal and pharyngeal activity, the frequency for the combination should be 31/21 times 34/21, multiplied by the frequency of organic disease in the general population (21 per cent) This product is 50 per cent, which is almost exactly the frequency observed The antagonism of the two signs among patients without organic disease of the brain is statistical rather than physiologic In the second combination, a similar situation prevails but is secondary in importance to a physiologic antagonism between an active pharyngeal reflex and an underactive abdominal reflex in the absence of organic disease of the brain This second combination is, therefore, a more reliable sign, as the tabulated data readily indicate

Since an inactive corneal reflex and an underactive abdominal reflex are each more significant of organic disease of the brain than their respective alternatives, it might be expected that the combination of these two responses would show a higher incidence of organic disease than any of the other three possible combinations The tabulated data are again confirmatory, a regular and orderly decrease in the percentage of organic disease is exhibited with progressive increase in activity of the abdominal reflex and with activity of the corneal reflex, whereas there is no trace of physiologic correlation between the two signs

4 *Relation of the Corneal and Pharyngeal Reflexes to Mayer's Phalangeal Sign* —The usefulness of Mayer's phalangeal sign is impaired by the appearance of either underactivity or overactivity in the presence of organic disease of the brain Monrad-Krohn [1] attributed pathologic significance only to loss of the reflex Wartenberg [5] conceded that although inactivity is a delicate pyramidal tract sign, the reflex may be absent in normal persons as well Further difficulty in interpretation is offered by exaggeration of the reflex "with a lesion of the frontomotor region of the brain" Ultimately, then, dependence on asymmetry

TABLE 4—*Distribution of Patients According to Mayer Reflex Activity and Corneal and Pharyngeal Responses*

		1	2	3	4	5	6	7	8	9
		Sum or Mean	C+	C—	P+	P—	C+ P+	C+ P—	C— P+	C— P—
A	Total patient series	74	18	26	23	51	14	34	9	17
B	Total number of patients without organic disease	46	34	12	8	38	6	28	2	10
C	Index of Mayer responses among patients without organic disease	109	112	100	212	87	200	93	250	70
D	Total number of patients with organic disease	28	14	14	15	13	8	6	7	7
E	Index of Mayer responses among patients with organic disease	164	100	228	160	169	75	133	257	200
F	Percentage of patients with organic disease among those with absence of or slight Mayer response	27	28	25	86	15	83	13	100	18
G	Percentage of patients with organic disease among those with moderate or strong Mayer responses	52	32	79	56	17	38	27	75	83
H	Percentage of patients with organic disease among total series of patients	38	29	54	65	25	57	18	78	41

remains, and even here, to quote Wartenberg further, "It may be extremely difficult to say on which side the reflex must be regarded as normal and on which as exaggerated or diminished"

From the data of table 4 inferences appear which may serve as reliable criteria in evaluating the Mayer response In lines C and E index numbers are given These indexes are computed by averaging values for 0, 100, 200 and 300 assigned to absence of reflexes and to slightly active, moderately active and extremely active reflexes, respectively First, it should be noted that the index for 46 patients without organic disease of the brain is 109, while the corresponding index for 28 patients with organic disease of the brain is 164 That is, our patients with organic disease of the brain showed, on the average, a more active Mayer reflex than the patients without organic disease of the brain (In the computations which appear in the table, the patients whose responses were bilaterally unequal, 9 of the patients without organic disease and 11 of the patients with organic disease, were each classified with respect to the more active of the two reflexes Classification according to the less active of the two reflexes yields a table with lower indexes but with essentially the same relations) This difference, which is significant only to the 6 per cent level (C R = 1 9), is not an important one but does confirm Wartenberg's observation that overactivity is as much a pathologic sign as underactivity and is probably more frequent

Further inspection of line C, columns 2, 3, 4 and 5, reveals that there is no difference in average activity of the Mayer response between groups of patients with an active corneal reflex and patients with an inactive corneal reflex However, the index of the activity of the Mayer reflex is much higher for patients with an active pharyngeal reflex than for patients with an inactive pharyngeal reflex, and the difference is significant to the 1 2 per cent level (C R = 2 5) In other words, among patients without organic disease of the brain, on the average, an active pharyngeal reflex implies an active Mayer reflex, and an inactive pharyngeal reflex implies an inactive Mayer reflex To this point, the values with respect to the Mayer reflex closely parallel those with respect to the abdominal reflex Among patients with organic disease of the brain (line E) there is no difference in average activity of the Mayer reflex between patients with an active pharyngeal reflex and patients with an inactive pharyngeal reflex However, there is a considerable difference in the average activity of the Mayer reflex between patients with an active corneal reflex and patients with an inactive corneal reflex, respectively, and this difference is significant to the 0 5 per cent level (C R = 2 8) Thus, among patients with organic disease of the brain, patients with an inactive

corneal reflex, on the average, exhibit an active Mayer response more frequently than those with an active corneal reflex

We are now in a position to formulate and test criteria for the interpretation of the Mayer reflex If among organically normal patients the activity of the Mayer reflex may be expected to vary with the activity of the pharyngeal reflex, then it is justifiable to infer that an inactive Mayer response in the presence of an active pharyngeal response is highly significant of disease of the brain On line F, columns 4 and 5, it is seen that 86 per cent of the patients in this series with an inactive Mayer reflex but with an active pharyngeal reflex have organic disease of the brain (6 of 7), as against 15 per cent of those with an inactive Mayer reflex and an inactive pharyngeal reflex (5 of 34), an inactive Mayer reflex is almost six times as significant for organic disease of the brain in the presence of an active pharyngeal response as in the presence of an inactive response (C R = 4 6) Line G reveals that an overactive Mayer response cannot be evaluated in terms of the pharyngeal response, since the incidence of organic cerebral disease is almost the same whether the pharyngeal reflex is active or inactive However, in this case, the corneal reflex becomes a useful criterion Among patients with an overactive Mayer response, organic disease of the brain is two and one-half times as frequent in the presence of an inactive corneal reflex as in the presence of an active corneal reflex, and this difference is highly significant (C R = 3)

The suggested criteria for interpreting the Mayer reflex may be stated as follows When the Mayer reflex is absent or is only slightly active, organic disease of the brain is highly probable if the pharyngeal reflex is active, when the Mayer reflex is extremely (or perhaps moderately) active, organic disease is highly probable if the corneal reflex is inactive

It will be recalled that in the preceding section a distinction was made between the combination of an inactive corneal and an active pharyngeal reflex, on the one hand, and an underactive abdominal and an active pharyngeal reflex, on the other The first pair suggests organic disease of the brain only because, on the basis of the incidence of the two signs taken individually, the combination is to be expected relatively infrequently in the absence of organic disease of the brain The second pair suggests organic disease of the brain, because in the presence of a normal brain there is the physiologic basis for a direct relation between activity of the abdominal and of the pharyngeal reflex, therefore any deviation from this relationship in the indicated direction suggests disease The data may now be examined to discover which type of relationship is the basis for the criteria we have just ascertained for interpretation of the Mayer reflex From line H, organic disease

appears to be 54/38 times as frequent in the presence of an inactive corneal reflex as in the total population From column 1, organic disease appears to be 52/38 times as frequent in the presence of an active Mayer reflex as in the total series One has a right, then, to expect, on the basis of probability alone, without necessarily inferring a physiologic relationship, that the combination of an inactive corneal and an active Mayer reflex will provide an incidence of organic disease equal to 54/38 by 52/38, multiplied by the incidence of organic disease in the general population (38 per cent) This product is 74 per cent, which agrees closely with the observed incidence of 79 per cent We must conclude that the inverse relationship between activity of the corneal reflex and activity of the Mayer reflex among patients with organic disease of the brain is a statistical one only Again, from line H, organic disease is 65/38 times as frequent in the presence of an active pharyngeal reflex as in the total population From column 1, organic disease is 27/38 times as frequent in the presence of an inactive Mayer reflex as in the total population Again, on the basis of probability alone, the incidence of organic disease of the brain in cases in which the Mayer reflex is inactive and the pharyngeal reflex active is expected to be 65/38 times 27/38, multiplied by the incidence of organic disease in the total population (38 per cent) This product is only 46 per cent, in contrast to the observed incidence of 86 per cent, a difference which is significant to the 0 9 per cent level (C R = 2 6) We must infer, therefore, that the pathologic significance of the inactive Mayer reflex in the presence of the active pharyngeal reflex depends not on statistical incidence but on a physiologic antagonism between these two values in the absence of organic disease of the brain

5 *Relation of the Corneal and Pharyngeal Reflexes to the Babinski Reflex*—Positive Babinski responses (extension of the large toe) were, of course, more frequent among our patients with organic disease of the brain than among the patients without organic disease of the brain There is not a sufficient number of frank positive responses in the series, however, to permit the type of analysis made in the case of abdominal and Mayer reflexes Nevertheless, the records include 42 patients with no response to plantar stimulation and 81 patients with the plantar flexor response Although it might have been expected, on the basis of analogy with the previously discussed phenomena, that similar relations with corneal and pharyngeal reflexes would appear, actually no correlations were even vaguely apparent The only possible exception to this is a somewhat suggestive association between absence of the plantar response and absence of the corneal reflex among patients with organic disease of the brain—an entirely statistical phe-

nomenon and one whose absence would be more surprising than its presence

6 *Relation of Corneal and Pharyngeal Reflexes to Deep Reflexes and the Hoffmann Reflex*.—It is fairly well established that a positive Hoffmann reflex is merely an exaggerated tendon reflex (Wartenberg[5]), our results are consistent with this thesis in that neither the deep reflexes nor the Hoffmann reflex showed any relation to either the corneal or the pharyngeal reflex. A population of 141 patients, of whom 21 per cent had organic disease of the brain, was available for study of deep, or tendon, reflexes. Of patients whose tendon reflexes seemed of about average activity, 6 per cent had organic disease of the brain, of patients with underactive reflexes, 14 per cent had such disease, of patients with diffusely overactive reflexes, 22 per cent exhibited signs of organic cerebral disease, and of patients with irregular distribution of tendon reflex activity, 33 per cent had organic disease of the brain. These ratios were not significantly different when patients were grouped according to the activity of their corneal and pharyngeal reflexes.

Of even greater interest is the fact that in the population here studied the Hoffmann response proved of no assistance in distinguishing cases of organic disease of the brain, since there was an equal proportion of patients with organic disease who exhibited positive and negative Hoffmann responses. No matter what type of analysis is employed, the data show nothing but a random distribution when the cross classification is made on the basis of Hoffmann response and the corneal or the pharyngeal responses. We agree categorically with Wartenberg's recent statement:

> It is essential to stress that however valuable a pyramidal sign the Hoffmann reflex may be, it is not itself pathologic, it indicates, if outspoken, only a state of increased muscular tonus, which may be pyramidal, but may also be purely functional, and therefore is diagnostically insignificant[5]

On the basis of these results, it may be inferred that exaggeration of the deep reflexes and a positive Hoffmann response, on the one hand, and absence of the abdominal reflex and the Mayer reflex, on the other, achieve their clinical significance by different mechanisms, although both groups of signs are considered indicative of damage to the pyramidal tract. This inference is consistent with recent experimental work[7]

7 *Relation of the Pharyngeal Reflex to Muscular Tonus*.—Muscular tonus was tested by estimating roughly the resistance offered to passive manipulation of the upper extremities and was recorded as normal (or,

7 Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

better still, average) and slightly, moderately or greatly increased or decreased Index numbers were constructed by averaging assigned values 0 for average tonus, 100, 200 and 300 for slightly, moderately and greatly increased tonus, respectively, and — 100, — 200 and — 300 for the three grades of diminished tonus Among the patients without organic disease of the brain, those with an active pharyngeal reflex averaged — 10 for tonus, and the group with an inactive pharyngeal reflex averaged + 44 This difference, while not sufficiently clearcut to be of clinical usefulness, is nevertheless significant to the 1 6 per cent level (C R = 2 4) No association with the corneal reflex was discernible

8 *Relation of the Corneal Reflex to Tremor* —The presence of tremor was tested for by inspection of the outstretched upper extremities and was recorded as absent, slight, moderate, marked Index numbers were constructed in the usual manner by assigning respective values of 0, 100, 200 and 300 to the four groups and averaging Among the patients without a diagnosis of organic disease of the brain, those with an active corneal reflex averaged 53, and those with an inactive corneal reflex averaged 91 As in the preceding paragraph, this difference is not sufficiently conspicuous to be of clinical value, but it does reach the level of significance of 1 6 per cent (C R = 2 4) No association with the pharyngeal reflex was evident

9 *Relation of Corneal Reflex to Spontaneous Motility* —Proceeding from the elementary and automatic fragments of behavior to its more complicated and derived aspects, estimations become less precise and correlations more equivocal The patient's spontaneous motility was rated on the basis of restlessness and frequency of random and purposive movements and was graded as normal or slightly, moderately or greatly increased or decreased Indexes were computed by the method described in section 7 Of 110 patients without organic disease of the brain, the average motility index for the group with active corneal reflexes is 69 and for the group with inactive corneal reflexes 29 Since this type of estimation is less precise than the grading of reflex responses, standard deviations are higher and the critical ratio in this instance is only 1 74, i e, the relationship is significant only to the 9 per cent level (odds for significance, 10 1) No definite conclusion can be drawn

10 *Relation of Corneal and Pharyngeal Reflexes to Clinically Estimated Aggressiveness* —After the psychiatric interview, each patient was recorded as aggressive, resistive or submissive in attitude toward the examiner This was done in the sanguine hope that an elementary fraction of behavior might thus be recorded Values of — 100, 0 and 100 were assigned to the three groups, respectively, and

indexes constructed as previously The index numbers for the four CP groups of patients without organic disease of the brain were 37, 62, 100 and 63, respectively The only difference apparent was that between the C + P + group and the other three groups taken together (average 65) However, computation revealed that the critical ratio for this difference is only 1 4, a value insufficient for the establishment of correlation

11 *Relation of the Pharyngeal Reflex to Autism*—Autistic phenomena, either hallucinatory or delusional, were recorded as none, slight, moderate or marked, and indexes were computed on this basis Of the patients without organic disease, those with an inactive pharyngeal reflex seemed to show, on the average, more autism than those with an active pharyngeal reflex, and computation here elicited a critical ratio of 2 1, i e, a level of significance of 3 per cent It is likely that this is the same correlation as was found between schizophrenic activity and obtundation of the pharyngeal reflex (section 2)

12 *Relation of Corneal and Pharyngeal Reflexes to Conversion Symptoms*—The problem of absence of the corneal and pharyngeal reflexes with conversion hysteria was one of the motivating factors in the organization of this study Since no patient was included for whom the sole diagnosis was conversion hysteria, the question could not be answered directly However, 21 patients out of 100 who were free from organic disease of the brain exhibited conversion phenomena as part of their symptoms The percentage incidence of these patients in the four CP groups is 30, 18, 0 and 24, no relationship between either the corneal or the pharyngeal reflex and conversion symptoms appears in this series

13 *Relation of Corneal and Pharyngeal Reflexes to Anxiety*—Anxiety, too, was regarded as a more or less elementary aspect of behavior, and it was estimated for each patient after psychiatric interview, on the basis merely of general impression The usual gradations and index numbers were assigned In addition, several of the somatic concomitants of anxiety, such as pulse rate, systolic, diastolic and pulse pressure, palmar sweating and hand temperature, were evaluated on a more exact basis The activity of the corneal and pharyngeal reflexes bore no relation either to anxiety or to any of these somatic factors

14 *Relation of Corneal and Pharyngeal Reflexes to Affect*—Affect was tentatively assumed to be a unitary aspect of behavior, and its quantitative variations were recorded and graded in the usual fashion The criteria employed in estimating variations were not definite but included the usual clinically evident data, such as the interest of the patient in his present situation, his enthusiasm with respect to plans for the future, facial mobility and vivacity of vocal expression Depres-

sive syndromes were classified with manic ones as forms of affective exaggeration An attempt was made to distinguish apprehensiveness and anxiety, such as appear frequently in catatonic patients, from true affective exacerbation or obtundation Obviously, the precision of these estimates could not be very high, and resultant coefficients of variation are considerable Nevertheless, among patients without organic disease of the brain the average rating of affect for the group with active pharyngeal reflex is —31, while for patients with inactive pharyngeal reflex the average rating of affect is — 123 This difference is significant to the 0 9 per cent level (C R = 2 6) It would seem, therefore, that there is an association between inactivity of the pharyngeal reflex and affective impairment, at least among the patients in this series

SUMMARY AND CONCLUSIONS

The pharyngeal reflex has been found to indicate the lower limit of normal activity for abdominal and Mayer reflexes Thus, in the absence of organic disease of the brain, an active pharyngeal reflex implies an active abdominal and an active Mayer reflex Similarly, in the presence of an inactive pharyngeal reflex, underactivity of the abdominal and Mayer reflexes is not necessarily indicative of disease

The concurrence of an active pharyngeal and an inactive corneal reflex and the concurrence of an overactive Mayer and an inactive corneal reflex have been found to be much less frequent among patients with organically sound brains than among patients with organic disease of the brain Thus, although these two combinations are not positive signs of abnormality, they are highly suggestive

Obtundation of the pharyngeal reflex is found to be statistically associated with an attitude some of the manifestations of which include affective blunting, autistic thinking and schizophrenic activity

Criteria for the interpretation of the Mayer reflex have been suggested Absence of or a weakly active Mayer response is indicative of a pathologic process if the pharyngeal reflex is active, a brisk Mayer response is usually indicative of a pathologic process if the corneal reflex is inactive

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HEREDITARY SCLEROSES

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THE term "heredofamilial" should be applied only to those diseases which are due to a change in the chromosomes which persists for several generations They may also be called heredodegenerative (Jendrassik[1]), since they all represent a minus variant Unlike these persisting changes of the chromosomes, the mutations, which cause heredofamilial diseases, the paravariations, originating under the influence of the surroundings, and the mixovariations, changes due to the union of two genes of different character are not hereditary

The properties of a man that are due to the structure of the idioplasm are called constitutional (genotypical, idiotypical) In addition to these inherited properties, there are others acquired in fetal life or after the birth, they were termed "conditional" by Tandler[2] The phenotypical man thus represents a combination of constitutional and conditional factors A factor of either type may lead to disease when it deviates from the norm When the constitutional factor prevails, amounting to 50 per cent or more, one speaks of a constitutional disease, to this type belong the heredodegenerative diseases The conditional diseases include, among others, various fetal diseases that lead to congenital, and even familial, disorders It should be emphasized that the terms "congenital" and "familial" do not mean heredofamilial, since congenital or familial diseases may also be caused by external factors

It is probable that mutations may occasionally be produced by chronic alcoholism or other poisoning and by physical forces (e g, roentgen rays) Yet such instances are too rare to account for the mutations in man in general In an attempt to find the cause of the mutations in amaurotic familial idiocy, I assumed, in view of the frequency of diabetes in the ancestry, that acidosis plays an important role Katase,[3] by feeding saccharose to rabbits, obtained various monsters in

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1 Jendrassik Die heredodegenerativen Nervenkrankheiten, in Lewandowsky, W Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol 2, p 231

2 Tandler, J Konstitution und Rassenhygiene, Ztschr f ang Anat **1** 11, 1913

3 Katase Experimentelle Studien uber die Entstehung des Hydrocephalus und die Entwicklungsanomalien des Auges, Tr Soc path japon **25** 583, 1935

the first, and even more in the second, filial generation and thus furnished evidence of a mutation due to acidosis

It is unlikely that disease is transmitted as such directly Rather, there is a change of the soma, with predisposition to a disease, but the various particular constitutions are not yet well understood No doubt the individual constitution, largely determined by the endocrine glands, plays a major role, leading to various generalized, metabolic and vascular trophic changes I [4] studied the endocrine constitution in cases of amaurotic familial idiocy and observed changes in the adrenal system and the thymus, resembling those described by other authors

A great difficulty in applying to man the rules of heredity in plants, as established by Johann Gregor Mendel [5] is the comparatively small number of children per subject Further, the inherited peculiarities are complicated in man, since they are due to changes in the chromosomes of many ancestors Hence, a comparison with the simple color changes in plants is not possible Finally, the diseased descendants may die in early childhood, without being able to produce a new generation

The only conclusion possible may be expressed as follows Different persons with similar constitutions under similar conditions may exhibit the same disease It is, further, more likely that similar constitutions will appear in two or more descendants of a consanguineous marriage, in which the parents may possess homologous genes, homozygotes, than in descendants of a marriage between persons of different ancestry (heterozygotes) Certainly, there are heredodegenerative diseases of the nervous system The factor of heredity may be dominant, that means the disease is the same in all affected generations, it may be recessive, i e, transmitted by a healthy parent, or it may be mixed Such diseases may, further, be sex bound, they may be of the same type (homotypic), they may occur at the same site (homotopic), and they may develop at the same time of life (homochronous) Particularly, the time-bound appearance of certain diseases is not easy to explain, since it does not always coincide with the various evolutional or involutional phases Certainly, however, the time factor is important in the constitution

Before applying the foregoing considerations to the heredofamilial scleroses, one has to establish the types of sclerosis that belong in this group Since scleroses represent glial proliferations replacing destroyed parenchyma, one should include in this term neither the tumor-like proliferations of mature tissue nor those of blastomatous tissue There-

4 Marburg, O The Endocrine Glands in Infantile Amaurotic Idiocy, J Nerv & Ment Dis **100** 450, 1944

5 Mendel, G Versuche uber Pflanzenhybriden, Verhandl naturf Ver in Brunn, 1865

fore Neuburger's [6] suggestion, accepted by other authors, that there are blastomatous, degenerative and inflammatory types of diffuse sclerosis, should be rejected, in agreement with Bielschowsky and Henneberg,[7] who assumed the existence of a degenerative and an inflammatory form only, the former being endogenous and the latter exogenous The familial occurrence of diffuse sclerosis is by no means evidence of a heredofamilial degeneration, for the simultaneous involvement of two or more members of a family may be caused not only by a constitutional but by an exogenous factor On the other hand, Guttmann [8] went too far in absolutely denying the existence of a degenerative form, which he assumed to be just a variant of the inflammatory type Suffice it to mention the investigations of Marburg and Casamajor [9] demonstrating the relationship of diffuse sclerosis to phlebostasis and phlebothrombosis, whereby a serous profusion may be the cause of the parenchymal destruction, followed by a sclerotic process Accordingly, scleroses are proliferations of glia which follow destruction of the myelin sheath, with comparatively well preserved axons

There are various types of scleroses, according to the distribution and the character of the disease In 1906 I [10] suggested calling acute sclerosis with demyelinating processes "encephalomyelitis periaxialis sclerotic ans" The principle of this terminology was accepted by Schilder [11] for diffuse sclerosis encephalomyelitis periaxialis diffusa Since there are degenerative and inflammatory forms, one should designate the degenerative forms as "encephalopathia periaxialis disseminata" and "encephalopathia periaxialis diffusa," respectively, and the inflammatory forms as "encephalomyelitis periaxialis disseminata" and "encephalomyelitis periaxialis diffusa," respectively These terms have not been accepted generally As for the inflammatory forms of acute multiple sclerosis, they are characterized by hyperemia, as well as by exudation from the blood vessels, associated with demyelination in the same region These manifestations justify calling the process inflammatory, a term which

6 Neuburger, K Histologisches zur Frage der diffusen Hirnsklerose, Ztschr f d ges Neurol u Psychiat **73** 336, 1921

7 Bielschowsky, M, and Henneberg, R Ueber familiare diffuse Sklerose (Leukodystrophia cerebri progressiva), J f Psychol u Neurol **36** 131, 1928

8 Guttmann, E Die diffuse Sklerose, Zentralbl f d ges Neurol u Psychiat **41** 1, 1925

9 Marburg, O, and Casamajor, L Phlebostasis and Phlebothrombosis of the Brain in Newborn and in Early Childhood, Arch Neurol & Psychiat **52** 170 (Sept) 1944

10 Marburg, O Die sogenannte akute multiple Sklerose (Encephalomyelitis periaxialis scleroticans), Leipzig, F Deuticke, 1906

11 Schilder, P (*a*) Zur Kenntnis der sogenannten diffusen Sklerose, Ztschr f d ges Neurol u Psychiat **10** 1, 1912, (*b*) Die Encephalitis periaxialis diffusa, Arch f Psychiat **71** 327, 1924

in this connection designates a histologic syndrome and does not indicate the etiologic factors (toxic, infectious or reactive) The same holds true for the acute form of diffuse sclerosis, as Schilder,[11] Bielschowsky and Henneberg[7] and others also stated It is not easy to establish whether the inflammatory process is primary or secondary (symptomatic)

Thus, one must distinguish the following groups of heredofamilial sclerosis.

Multiple sclerosis { (*a*) Encephalopathia periaxialis disseminata; (*b*) Encephalomyelitis periaxialis disseminata

Diffuse sclerosis { (*a*) Encephalopathia periaxialis diffusa; (*b*) Encephalomyelitis periaxialis diffusa (Schilder's disease)

Combined sclerosis

Pelizaeus-Merzbacher disease (degenerative form only)

MULTIPLE SCLEROSIS

About 100 cases of the familial type have been observed, in most of which no pathologic examination was made The majority of cases were instances of the familial type only, not the heredofamilial disease Only 4 cases were instances of the heredofamilial type 1 case reported by Eichhorst[12] (mother and son), later, another case from the same author,[13] in which the mother of the patient had spastic spinal paralysis, a case reported by Haber[14] (brother and sister, the parental grandmother of whom had a disease of the spinal cord), and a case reported by Thomas[15] (mother and daughter) studied pathologically by Gournand[16] It is impossible to recognize a particular type of heredity in these cases Unfortunately, these authors merely mentioned the anatomic picture of multiple sclerosis, without going into details Gournand,[16] alone, clearly demonstrated acute multiple sclerosis in the case of Thomas[15]

DIFFUSE SCLEROSIS

Einarson and Neel,[17] as well as Bielschowsky and Henneberg,[7] distinguished the following types of heredodegenerative (familial) diffuse sclerosis (*a*) acute infantile (Krabbe[18]), (*b*) subacute juvenile (Scholz[19]), (*c*) adult (Ferraro[20]) and (*d*) chronic (Pelizaeus,[21] Merzbacher[22])

12 Eichhorst, H Ueber infantile und hereditare multiple Sklerose, Virchows Arch f path Anat **146** 173, 1896

13 Eichhorst, H Multiple Sklerose und spastische Spinalparalyse, Med Klin **40** 1617, 1913

14 Haber, T Kasuistische Mitteilung zur Frage des hereditaren Auftretens der multiplen Sklerose, Monatschr f Psychiat **51** 226, 1922

15 Thomas, A Sclérose en plaqûes chez mere et la fille, Rev neurol **2** 714, 1929

16 Gournand, A La sclérose en plaques aigue, Paris, A LéGrand, 1930

17 Einarson, L, and Neel, A V Notes on Diffuse Sclerosis, Diffuse Gliomatosis and Diffuse Glioblastomatosis of the Brain, with a Report of two Cases, Copenhagen, Einar Munksgaard, 1940

(Footnotes continued on next page)

The number of cases of heredofamilial and familial diffuse sclerosis is comparatively small Van Bogaert and Scholz [23] found only 15 cases of the familial type, involving 5 families, among 70 cases of diffuse sclerosis In reviewing the literature, I found the acute infantile type in 7 families 2 cases of Krabbe,[18] 1 case of Van Bogaert and Scholz,[23] 1 case of von Eiselsberg,[24] 1 case of Russel and Tallermann,[25] 1 case of de Lange [26] and 1 case of Josephy and Lichtenstein [27] (though in the last case the disease was not acute) The subacute juvenile type was present in 9 families the cases of Haberfeld and Spieler,[28] Schilder,[11b] Scholz,[19] Bielschowsky and Henneberg,[7] Symonds [29] (2 families), Curtius,[30] Walthard [31] (case in the same family as that of Scholz) and Meyer and Tennent [32] (2 families) Of the adult type only Ferraro's [20] cases are

18 Krabbe, K A New Familial, Infantile Form of Diffuse Brain Sclerosis, Brain **39** 74, 1916

19 Scholz, W Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiarer diffuser Hirnsklerose im Kindesalter, Ztschr f d ges Neurol u Psychiat **99** 651, 1925

20 Ferraro, A Familial Form of Encephalitis Periaxialis Diffusa, J Nerv & Ment Dis **66** 329, 479 and 616, 1927

21 Pelizaeus, E Ueber eine eigentumliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditarer Grundlage (multiple Sklerose), Arch f Psychiat **16** 201, 1885, **31** 100, 1899

22 Merzbacher, L Eine eigenartige familiar-herditare Erkrankungsform (Aplasia axialis extracorticalis congenita), Ztschr f d ges Neurol u Psychiat **3** 1, 1910

23 van Bogaert, L, and Scholz, W Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiaren diffusen Sklerose, Ztschr f d ges Neurol u Psychiat **141** 510, 1932

24 von Eiselsberg, F Ueber fruhkindliche familiare diffuse Hirnsklerose, Ztschr f Kinderh **58** 702, 1937

25 Russel, D, and Tallermann, K Familial Progressive Diffuse Cerebral Sclerosis of Infants, Arch Dis Childhood **12** 71, 1937

26 de Lange, C Ueber die familiare infantile Form der diffusen Hirnsklerose, Ann pædiat **154** 140, 1939-1940

27 Josephy, H, and Lichtenstein, B W Diffuse Leukoencephalopathy Without Sclerosis, Arch Neurol & Psychiat **50** 575 (Nov) 1943

28 Haberfeld, W, and Spieler, F Zur diffusen Hirn- und Ruckenmarksklerose im Kindesalter, Deutsche Ztschr f Nervenh **40** 436, 1910

29 Symonds, O P A Contribution to the Clinical Study of Schilder's Encephalitis, Brain **51** 24, 1928

30 Curtius, F Familiare diffuse Sklerose und familiare spastische Spinalparalyse in einer Sippe, Ztschr f d ges Neurol u Psychiat **126** 209, 1930

31 Walthard, K M Familiare diffuse Hirnsklerose, Schweiz Arch f Neurol u Psychiat **32** 251, 1933

32 Meyer, A, and Tennent, T Familial Schilder's Disease, Brain **59** 100, 1936

known, and, in addition, the case of a family reported by van Bogaert and Nyssen [33] Finally to the chronic type belong the cases of Pelizaeus [21] and Merzbacher [22], in the same family, the cases of Spielmeyer [34] and of Liebers,[35] and a case of Bodechtel [36] In the cases enumerated, autopsy was performed on at least 1 member of the family On the whole, this is a relatively small figure as compared with the number of cases of the nonfamilial disease

Heredity—In cases of the disease in early childhood, though occurring in a familial manner, no specific heredity is exhibited There are no nervous diseases among the ascendants The same holds true for the adult type In cases of the juvenile type a nervous disease may be present in one of the parental generations, in addition, there may be a history of alcoholism or tuberculosis The latter conditions are occasionally also observed in the ascendants in cases of the infantile type Scholz [19] first reported the occurrence of spastic spinal paralysis in a parental generation, the first filial generation was free of nervous diseases, in the second filial generation diffuse sclerosis appeared However, Scholz [19] was not absolutely sure about the diagnosis of spastic spinal paralysis This same disease was described among the ascendants by Curtius [30] Whereas Scholz [19] did not exclude the possible diagnosis of multiple sclerosis, Meyer and Tennent [32] described with certainty the occurrence of multiple sclerosis among the ascendants In any case, diffuse sclerosis exhibits recessive heredity, so that the disease causing the heredofamilial degeneration has not yet been revealed It probably belongs to the sclerosis group The only type of diffuse sclerosis with definite heredity is Pelizaeus-Merzbacher disease The heredity resembles that of hemophilia, the disease is transmitted from a healthy female with a diseased brother to males in the filial generation Since not all familial disorders are heredodegenerative, the number of cases of true heredodegenerative diffuse sclerosis is even smaller than the number of the familial type

Structure—Schaffer [37] stressed that structure analysis is necessary to classify a case of sclerosis as of the heredofamilial type Thus, I

33 van Bogaert, L, and Nyssen, R Le type tardif de leukodystrophie familiale, Rev neurol **65** 21, 1936

34 Spielmeyer, W Der anatomische Befund in einem zweiten Fall von Pelizaeus-Merzbacherscher Krankheit, Zentralbl f d ges Neurol u Psychiat **32** 203, 1923

35 Liebers, M Zur Histopathologie des zweiten Falles von Pelizaeus-Merzbacherscher Krankheit, Ztschr f d ges Neurol u Psychiat **115** 487, 1928

36 Bodechtel, G Zur Frage der Pelizaeus-Merzbacherschen Krankheit, Ztschr f d ges Neurol u Psychiat **121** 487, 1939

37 Schaffer, K Ueber das morphologische Wesen und die Histopathologie der herditar-systematischen Nervenkrankheiten, Berlin, Julius Springer, 1926

studied 2 cases,[38] 1 of type *a* and another of type *b*, and found the most striking feature to be the extension of the process, the diffuse demyelination of the centrum ovale There is, however, a wide range of variations Occasionally almost the entire white matter is affected (fig 1 *A*), from the frontal to the occipital lobe, as in the case of Meyer and Tennent [32], in other cases some lobes are spared One must agree with Bouman [39] that the occipital, parietal and temporal regions are more frequently affected than is the frontal region There may be patches of complete demyelination (fig 1 *B*), in other cases there is the picture of foci of myelin shadows, and concentric demyelination has been reported On

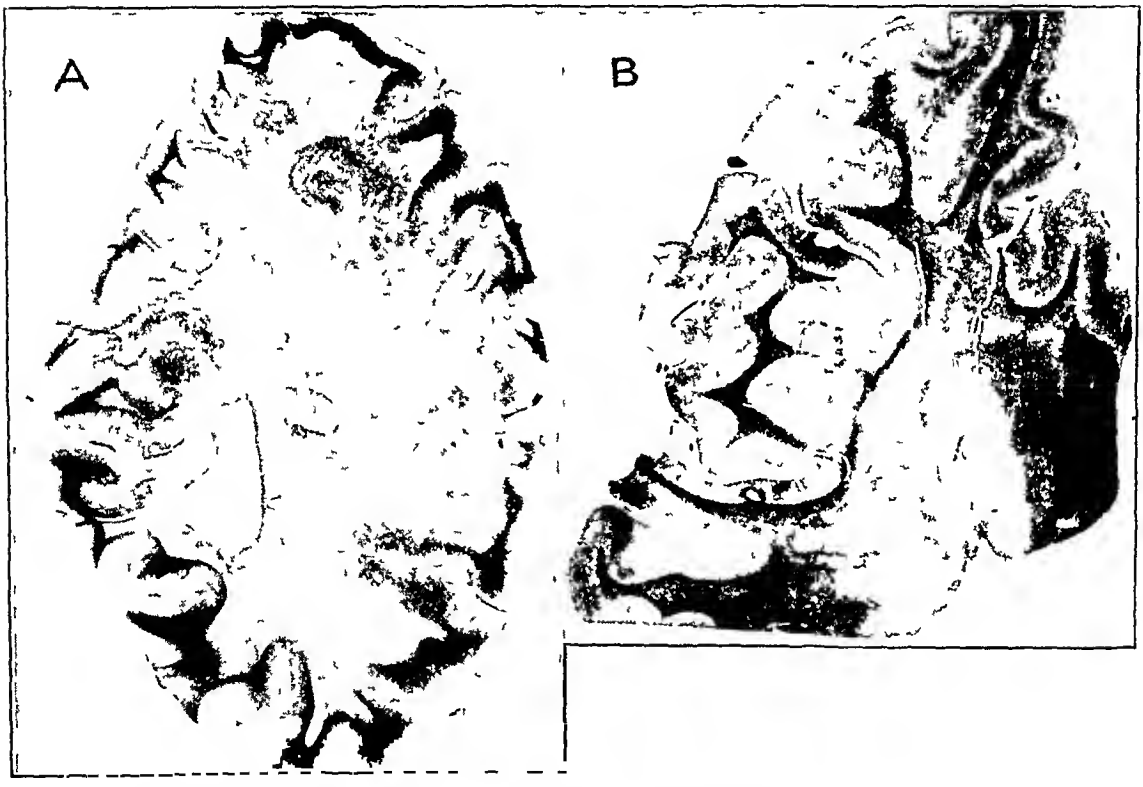

Fig 1.—*A* (case 2), diffuse sclerosis, with U fibers intact *B* (case 1), diffuse sclerosis (type of Krabbe), with two large foci

accurate examination one will find, in addition to large areas of demyelination, small ones at the periphery, resulting in a pathologic picture resembling that of multiple sclerosis, in spite of the presence of large areas of destruction The resemblance to multiple sclerosis is also indicated by the persistence of single myelin fibers or of groups of such fibers within the large foci In some cases the demyelination presents

38 The cases referred to which I reinvestigated were those of von Eiselsberg (case 1) and Pfleger (case 2) (Jahrb f Psychiat u Neurol **50** 142, 1933)

39 Bouman, L Diffuse Sclerosis, Bristol, John Wright & Sons, Ltd, 1934

sharp borderlines, in others there is a gradual transition into normal tissue, in which the border fibers may be swollen or present a rosary-like appearance, or they may be partly degenerated

Most authors have stressed the intactness of the U fibers (fig 1 *A*), which is observed in many cases Occasionally, however, the ring of the U fibers is perforated at one point or another Nevertheless, the picture of intact U fibers, with a normal overlying cortex, is characteristic

It is not only the centrum ovale which is affected In many cases the striopallidum (von Eiselsberg,[24] Russel and Tallermann [25]) and the optic thalamus (Liebers [35]) show similar lesions, and frequently the optic nerve is also involved (Krabbe,[18] Scholz,[19] Bielschowsky and Henneberg,[7] Russel and Tallermann,[25] Ferraro [20] and others) The cerebellum frequently is the site of a focus (Russel and Tallermann,[25] Ferraro [20]), and the brain stem, as well as the spinal cord, may be affected (von Eiselsberg,[24] Russel and Tallermann,[25] de Lange [26]) Thus, in most cases the disease approaches multiple sclerosis as far as the distribution of lesions is concerned In the cases with localization in the brain stem, as well as in cases with foci in the centrum ovale, sometimes sharp, sometimes hazy, borderlines are observed

In spite of the total demyelination, a number of axons, though usually few, may be relatively well preserved Their number depends on the character of the focus In an acute process, indicated by the presence of many compound granular cells, one finds comparatively many intact axons, in foci with far advanced sclerosis or with regressive changes no axons are encountered In many cases, however, the destruction of the myelin sheaths is not commensurate with that of the axons, which may disappear even in cases of the chronic (Pelizaeus-Merzbacher) type Some foci, particularly those in the optic chiasm, closely resemble the foci of multiple sclerosis (Liebers [35])

There are areas deprived almost completely of oligodendrocytes, the few present are degenerated (fig 2) The ground substance is represented by a fine network of glial fibrils In other areas there are giant astrocytes around a blood vessel, these cells are occasionally deprived of their processes In general, the number of these giant cells is smaller than normal (fig 3) At the border zones of the areas of sclerosis there is an increase in the number of the glia cells, some of which resemble the fetal cells of the sixth month, as depicted in Roback and Scherer's [40] paper on glial development (fig 4) In this peripheral region one also encounters multinuclear cells (fig 5), fibril-

40 Roback, H N, and Scherer, H J Ueber die feinere Morphologie des fruhkindlichen Gehirns mit besonderer Berucksichtigung der Gliaentwicklung, Virchows Arch f path Anat **294** 365, 1935

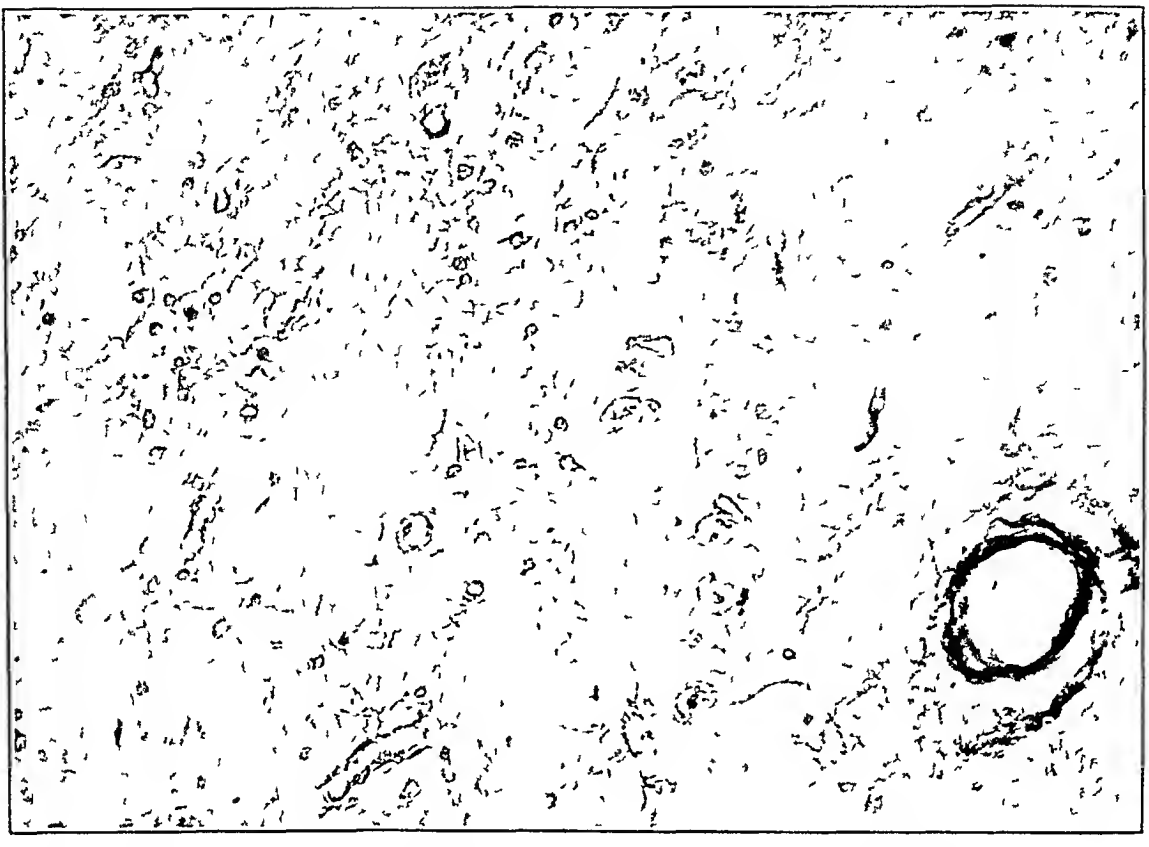

Fig 2 (case 2) —Disappearance of oligodendroglia cells, vascular sclerosis

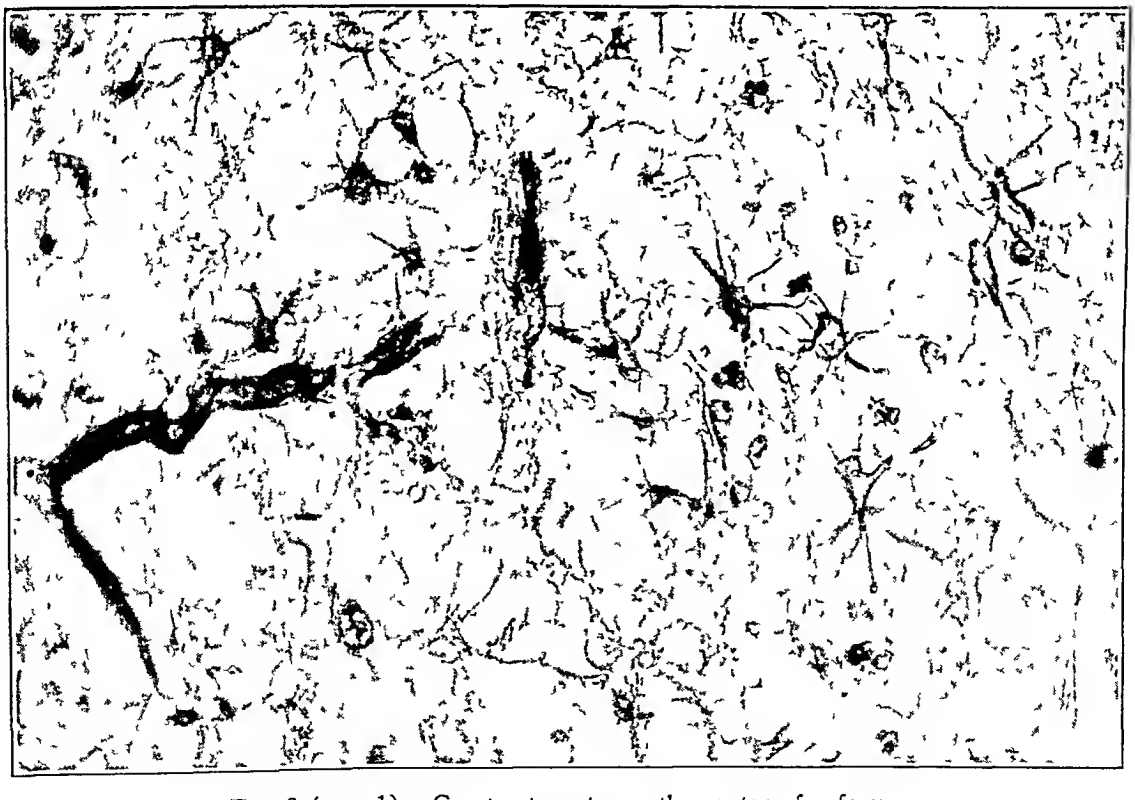

Fig 3 (case 1) —Giant astrocytes in the center of a focus

lary astrocytes and numerous compound granular cells Cells of the last type are also seen in any fresh focus Some of the large glia cells are transformed into *gemastete* cells (globoid cells), with small vacuoles in the cell body

Though there are many signs of destruction of the glia, there is not an insufficiency of the glia as a whole, nor is there a clear manifestation of the existence of an endogenous process, as was assumed by Bielschowsky and Henneberg [7] and de Lange,[26] since exogenous causes may furnish a satisfactory explanation of the pathologic changes In particular, there is no complete lack of the oligodendroglia, which was assumed by Collier and Greenfield [41] This tissue is absent only in areas of complete disintegration Further, contrary to the suggestion of Bielschowsky and Henneberg,[7] there is no insufficiency of the constructive apparatus, since there is intense fibrillogenesis, leading to anisomorphous sclerosis Multinuclear glia cells, which, in the opinion of many authors, are evidence that these scleroses approach tuberous

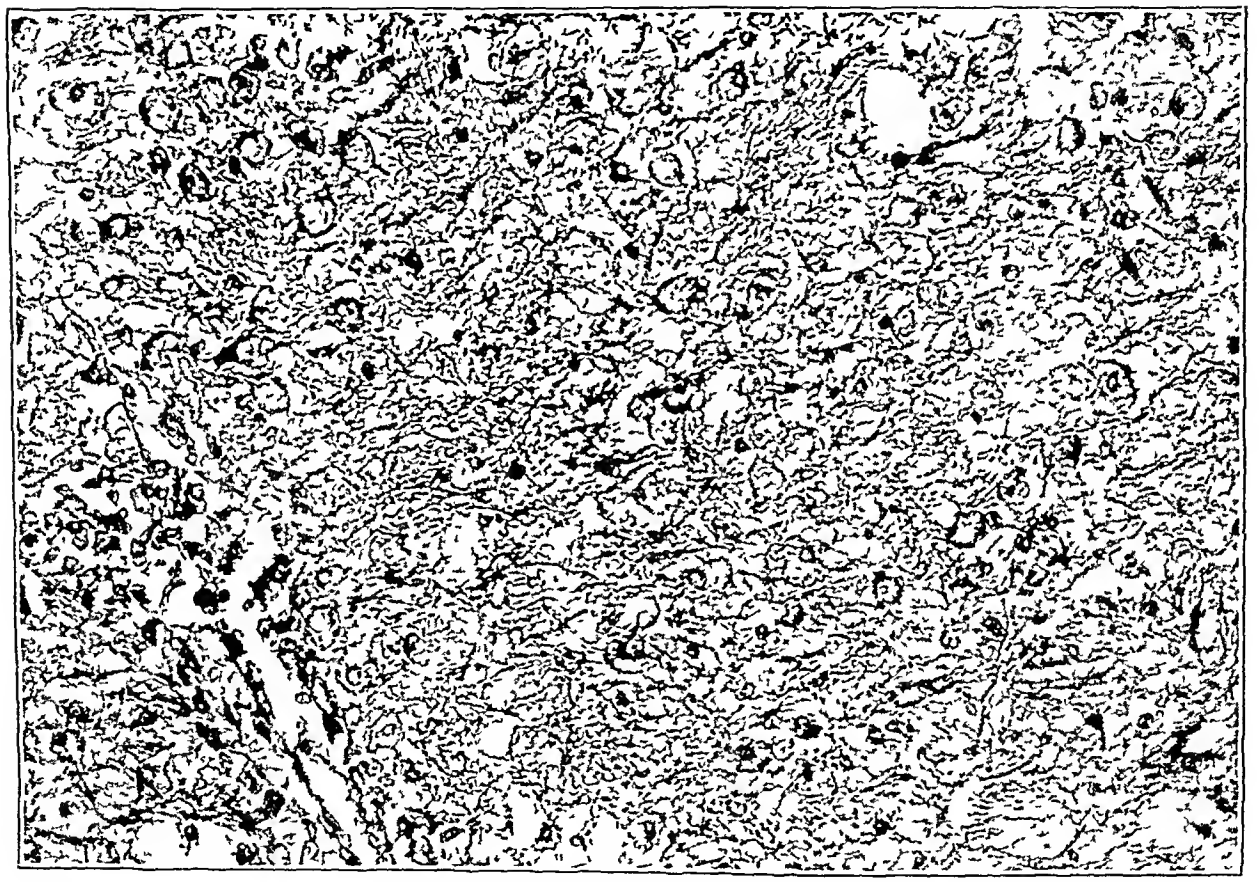

Fig 4 (case 2) —Accumulation of different types of glia cells (fetal, globoid and compound granular)

41 Collier, G, and Greenfield, I G The Encephalitis Periaxialis of Schilder, Brain **47** 489, 1924

sclerosis may be encountered also in cases of acute multiple sclerosis, together with globoid cells (*gemastete* cells)

The reaction of the mesoderm varies with the type of sclerosis In the juvenile type there are perivascular infiltrations of lymphocytes, and occasionally of plasma cells This exudate is the same as that described by me [10] in association with acute multiple sclerosis, and by Schilder [11a] with diffuse sclerosis It depends on the point of view whether one

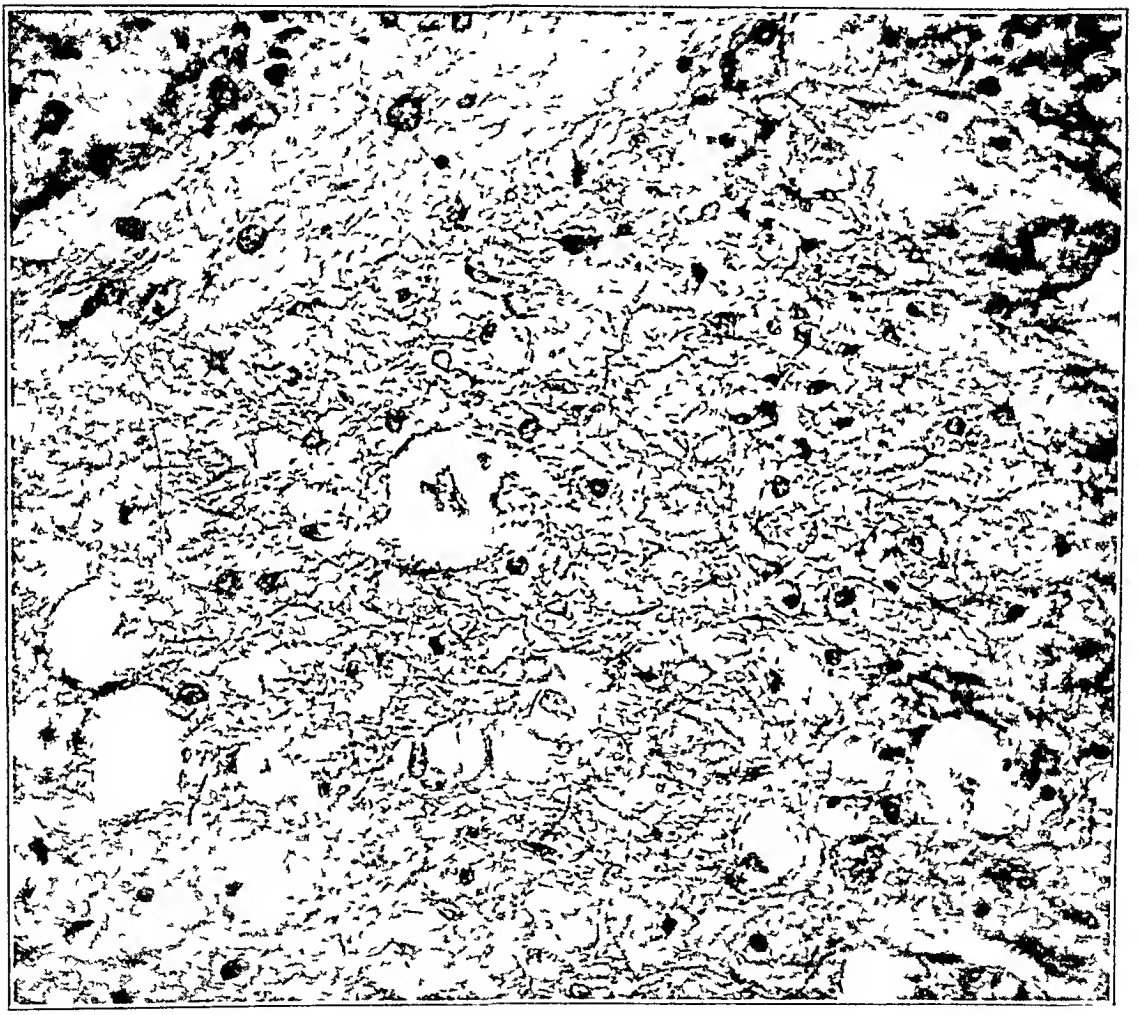

Fig 5 (case 2) —Multinuclear glia cells

calls the process symptomatic inflammation (Scholz [19]) or true inflammation (Meyer and Tennent,[32] in agreement with Haberfeld and Spieler [28] and Schilder [11a]) The changes in the vessel walls have scarcely been described In regions close to the scleroses one encounters empty veins, the lumens of which are narrow in some places, as though contracted In other areas the lumens are wide but empty (fig 6) In necrotic areas some vessel walls are degenerated (fig 2),

obviously a secondary feature The pictures resemble those in cases of birth injury with phlebastosis and phlebothrombosis, as described by Casamajor and me [9] Putnam and Alexander [42] also saw phlebothrombosis in cases of diffuse sclerosis

Comment In summary, one may state There is usually a bilaterally symmetric, demyelinating process in the centrum semiovale, followed by sclerosis, with participation of glia cells, which show different stages of progressive and regressive changes, depending on the state of the vascularization The process is not always restricted to the

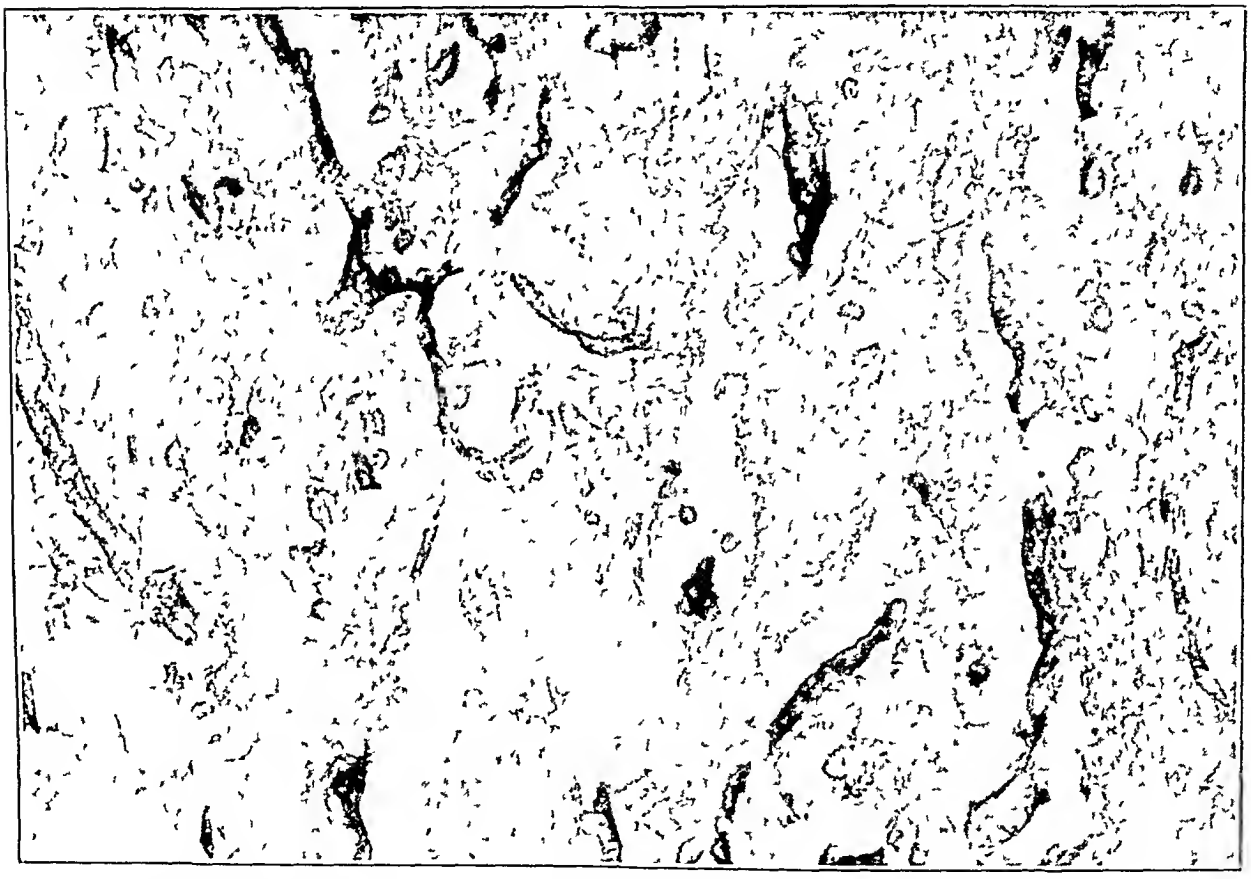

Fig 6 (case 2) —Veins close to a focus, empty and contracted at one spot, enlarged nearby

centrum semiovale but occasionally affects also the striopallidum, the optic nerve and even the brain stem and the spinal cord The character of the process is degenerative and occasionally inflammatory Thus use of the terms encephalomyelopathia peraxialis diffusa and encephalomyelitis peraxialis diffusa is justifiable, whereas the designation "scleroticans" describes the pathologic process

42 Putnam, T J, and Alexander, L Disseminated Encephalomyelitis A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch Neurol & Psychiat **41** 1087 (June) 1939

Pathogenesis.—It is difficult to assume with Schilder [11a] an inflammatory process in the genesis of hereditary diffuse sclerosis, since the possibility of the transmission of such a process through generations is doubtful. Another view assumes an insufficiency of the oligodendroglia in the production of myelin. However, aside from the fact that usually the axons also are destroyed, it is known from the investigations of Roback and Scherer [40] that the immature glia aids in the process of myelination. Whereas Scholz [19] asserted that there was an insufficiency of all glia cells, Bielschowsky and Henneberg [7] upheld the theory of an insufficiency of the entire vascular, as well as the glial, constructive apparatus. This theory leaves unexplained why such a disturbance of the entire constructive apparatus becomes effective only in certain circumscribed areas and not throughout the neuraxis. None of the authors mentioned noted that the peculiar distribution of the foci is associated with the area of drainage of the great vein of Galen (Schwartz,[43] Schlesinger [44]). My investigations in collaboration with Casamajor [9] have demonstrated that phlebostasis and phlebothrombosis in the great vein of Galen lead to destruction of these areas, with subsequent sclerotic processes and with intactness of the U fibers. This theory receives support also from case 3 of Globus and Strauss [45]. The sister of the patient (in the same disease) showed (venous) thrombosis of the sinuses throughout the brain.

Not a single case of diffuse sclerosis is known in which the disease occurred in the ascendants, so that in this disease it is particularly true that "familial" does not mean "heredodegenerative." Type *a* (Krabbe) may be explained by conditional rather than by constitutional factors, while the constitutional factor cannot be excluded in type *b*. Guttmann and Bodechtel [46] and Guttmann [8] did not differentiate these two types.

Wohlwill [47] (1921) first showed that a process in the veins may cause areas of destruction and demyelination resembling those in diffuse sclerosis. In 1928 he [48] suggested that some dissolved, harmful sub-

43 Schwartz, P. Die traumatischen Schadigungen des Zentralnervensystems durch die Geburt. Anatomische Untersuchungen, Ergebn. d. inn. Med. u. Kinderh. **31**: 165, 1927.

44 Schlesinger, B. The Venous Drainage of the Brain, with Special Reference to the Galenic System, Brain **62**: 274, 1939.

45 Globus, J. H., and Strauss, I. Progressive Degenerative Subcortical Encephalopathia, Arch. Neurol. & Psychiat. **20**: 1190 (Dec.) 1928.

46 Guttmann, E., and Bodechtel, G. Diffuse Encephalitis mit sklerosierender Entzundung des Hemispharenmarkes, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**: 601, 1931.

47 Wohlwill, F. Zur Frage der Encephalitis congenita (Virchow), Ztschr. f. d. ges. Neurol. u. Psychiat. **73**: 360, 1921.

48 Wohlwill, F. Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**: 20, 1928.

stances may diffuse into the nerve tissue, thus causing demyelination In 1931 Putnam [49] and his co-workers stressed the importance of phlebothrombosis in demyelinating processes Finally, Casamajor and I [9] demonstrated that phlebospasm may have the same effect It may be that the process of diffusion is caused by the same change as is the venous spasm, viz, by the previous enlargement of the vessels, according to Ricker's [50] *Phasengesetz* Thus, three different circulatory changes in the venous system may lead to a similar effect phlebodilatation (prestasis) with diffusion, phlebothrombosis and phlebospasm These circulatory changes are sufficient to account for the process as a whole, so that it is not necessary to assume a heredodegenerative factor One should, however, attempt to determine the constitutional factors in this disease, which probably will disclose the cause of the venous changes As for the endocrine constitution, there are some cases of amaurotic familial idiocy (Bielschowsky,[51] Globus,[52] Flatau,[53] Ostertag [54]) with demyelinations resembling those in diffuse sclerosis One would, however, be mistaken in assuming an essential relationship between these two diseases On the other hand, amaurotic familial idiocy may be complicated by involvement of the centrum ovale Since the endocrine constitution in patients with amaurotic familial idiocy is complicated (one encounters destruction of the adrenal medulla, changes in the thymus and involvement of the intermediate cells of the gonads), and since nothing is known about these glands in cases of diffuse sclerosis, it is difficult to draw definite conclusions Hampel [55] was the only one to observe a case of Addison's disease associated with a demyelinating process in the hemispheres There are some clinical fea-

49 Putnam, T J Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch Neurol & Psychiat **37** 1298 (June) 1937 Putnam, T J, McKenna, J B, and Morrison, L R Studies in Multiple Sclerosis I The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J A M A **97** 1591 (Nov 28) 1931

50 Ricker, G, and Regendanz, P Beitrage zur Kenntnis der ortlichen Kreislaufstorung, Virchows Arch f path Anat **231** 1, 1921

51 Bielschowsky, M Zur Histopathologie und Pathogenese der amaurotischen Idiotie, J f Psychol u Neurol **26** 125, 1920-1921

52 Globus, J H Ein Beitrag zur Histologie der amaurotischen Idiotie, Ztschr f d ges Neurol u Psychiat **85** 424, 1923

53 Flatau, E Encephaloleucopathia scleroticans progressiva, Encephale **20.** 475, 1925

54 Ostertag, R Amaurotische Idiotie mit Entwicklungsstorungen des Gehirns und Kleinhirnatrophie, Centralbl f Neurol **39** 190, 1925, Arch f Psychiat **75** 355, 1925

55 Hampel, E Morbus Addisonii und sklerosierende Erkrankung des Hemispharenmarks Beitrag zu den Hirnveranderungen beim Morbus Addisonii und zum Kapitel der diffusen Sklerosen, Deutsche Ztschr f Nervenh **142** 186, 1937

tures (e g, hirsutism) that also point to involvement of the adrenal system However, these changes are of too slight a degree to be used as a basis for discussion of the relationship between the adrenal system and the changes in the venous system

Pelizaeus-Merzbacher disease is now assumed to be a combination of diffuse and multiple sclerosis, there are, however, no reports on changes in the vascular system

SUMMARY

Familial diseases may, but need not, be heredofamilial Heredofamilial diseases are caused by mutations alone

As for the scleroses, multiple sclerosis usually is an exogenous disease, though there are certainly cases of the heredofamilial type

The infantile form of diffuse sclerosis does not exhibit any evidence of being heredofamilial The juvenile form may be heredofamilial, or it may be exogenous, whereas Pelizaeus-Merzbacher disease apparently always is heredofamilial

In all the types under discussion, a change in the venous system (phlebostasis, phlebothrombosis, phlebospasm) may be the cause of demyelination The cause of the venous change itself has not yet been revealed

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NARCOLEPSY

II Theory of Pathogenesis of the Narcolepsy-Cataplexy Syndrome

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IN a careful review of the literature on narcolepsy, Wilson [1] found that authors had classified narcolepsy according to the following etiologic factors (1) trauma, (2) toxi-infectious states, such as encephalitis, (3) epilepsy, (4) endocrine disturbances, such as obesity, (5) psychopathologic disturbances, (6) local lesions (vascular lesions, tumor), and (7) cryptogenic conditions He criticized these categories because they were not mutually exclusive, because presumably "predisposing" factors may be only accompaniments and because the influence of trauma can be overrated He argued, further, that autopsy had not been performed in any case to ascertain the existence of such groups and that pathologic information at one's disposal was derived from cases of prolonged or continuous sleep and not from cases of the true narcolepsy-cataplexy syndrome Therefore, although many researches tended to point to the floor, sides and posterior end of the third ventricle as a part of the neuraxis the mechanisms of which are engaged in the function of sleep,[2] he abandoned the search for the cause of narcolepsy in discrete lesions in this region He pointed out that sleep is such a complex process that to imagine that motor, sensory, psychic, respiratory, circulatory and other activities are all controllable by one ganglionic center in the hypothalamus puts a strain on physiologic belief He concluded that the hypothalamic center could best be regarded as serving to control viscerosympathetic activities which must diminish for sleep to set in, but that the cortex and thalamus had to cooperate to bring sleep about

WILSON'S FORMULATION

Wilson abandoned all former speculations concerning the cause of narcolepsy because of their inherent deficiencies In making his own formulation he began with the premise that any explanation of the pathogenesis of the disorder must bring the apparently diverse phenomena of narcolepsy cataplexy, sleep paralysis and catalepsy (trance)

1 Wilson, S A K Neurology, edited by A N Bruce, London, Edward Arnold & Co, 1940

2 Wilson, S A K The Narcolepsies, Brain **51** 63-109, 1928, Modern Problems in Neurology, London, Edward Arnold & Co, 1928

into line, since the clinical fact of the common existence of these various disorders in the patient dictated it His concept of the cause of the syndrome, although it contains deficiencies, which he points out, strives toward that end

He began with cataplexy and stated that it evidently is not pathologic but is akin to what can be found on occasion in normal persons or in animals As a sequel to emotional stimuli, of which perhaps the commonest is laughter, one may be "convulsed" or made "weak" or "helpless" Animals, though they lack the gift of laughter for the most part, may become "rooted to the spot" or "frightened out of their lives" in sudden fear, or they may run away Thus the affective stimulus either excites or inhibits, or inhibition succeeds excitation Wilson went on to say that, for some ill understood reason, in the case of cataplexy such stimuli seemed invariably to inhibit

He found the attack of sleep paralysis of the narcoleptic person similar to the cataplectic attack The same kind of inhibition spreading to the motor area, but not radiating to the cortical fields involving consciousness, must be assumed to account for the fact that the patient is awake though powerless He viewed the trancelike cataleptic state seen in the narcoleptic patient as a lesser degree of inhibition radiating over the cortex, in which movement was inhibited not to the point of atonia, as in patients with catalepsy or sleep paralysis, but to the point of modification of plastic tone, i e, catatonia As for the fits of deep sleep, the narcoleptic attacks, he regarded them as a more extensive radiation of inhibition throughout the cortex, spreading down the neuraxis through the thalamus and the hypothalamic areas In all this he used the view of Pavlov [3] that sleep is internal inhibition diffused continuously over the cortex and descending also to lower parts of the brain

Wilson's formulation of the phenomena seen in the narcoleptic patient as manifestations of varying degrees of radiation of internal inhibition (Pavlov) may be summarized as follows

1 Trancelike states (catalepsy)
   (*a*) Partial spread of internal inhibition to the motor cortical area, producing a partial alteration of movement and plastic tone, or catatonia
   (*b*) No spread to cortical fields involving consciousness in the usual case
2 Cataplexy
   (*a*) Total spread of internal inhibition to the motor cortical area, producing total loss of movement and tone (which are

3 Pavlov, I P Conditioned Reflexes An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G V Anrep, London, Oxford University Press, 1927

one and the same, according to Sherrington), or atonia, and consequent falling to the ground

(*b*) No spread to cortical fields involving consciousness

3 Sleep paralysis

(*a*) Total spread to the motor cortical area, producing atonia, as in cataplexy, but without falling, since the patient is in the sleeping position

(*b*) Spread of internal inhibition to the "edge of the cortical fields of consciousness," if such a term can be used, since this phenomenon occurs on the "edge" of sleep, whether incipient or emergent

4 Narcolepsy

(*a*) Spread of internal inhibition throughout the motor cortex and down the neuraxis to the levels of postural and viscero-sympathetic control in the brain stem and the hypothalamus, leading to the pattern of motility of somatic and visceral muscle found in true sleep

(*b*) Spread of internal inhibition through the cortical and thalamic fields of consciousness, leading to the psychic phenomena of true sleep

Justification for the contention that the motor cortex is suspended or inhibited in activity during both sleep and cataplexy is found in the fact that plantar stimulation produces the pathologic sign of Babinski in both states In sleep this phenomenon is well known, and Wilson [2] found it in cataplexy as well The similarity of the cortical mechanism in true sleep and in narcoleptic sleep is given support by recent electro-encephalographic studies Cohn and Cruvant [4] found that the patterns of the brain waves in sleep and in the narcoleptic attack are similar in configuration, a fact which suggests the fundamental physiologic similarity in the cortex in the two states What are the deficiencies in such a formulation? The following questions may be posed

1 What is the peculiar quality of emotional stimuli which produces cataplexy?

2 What as Wilson asks, is the ill understood reason that emotional stimuli should invariably cause inhibition of motility and tone in cataplectic attacks?

3 Can the apparently diverse phenomena of narcolepsy, cataplexy, sleep paralysis and catalepsy (trance) be kept in line in any elaboration made on the formulation?

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4 Cohn, R, and Cruvant, B A Relation of Narcolepsy to the Epilepsies A Clinical-Electroencephalographic Study, Arch Neurol & Psychiat **51** 163 (Feb) 1944

4 What is it about the brain of the narcoleptic patient that makes it so susceptible to manifestations of inhibition?

THE "ULTRAPARADOXIC PHASE" OF PAVLOV

The second volume of translations of Pavlov's writings into English, "Conditioned Reflexes and Psychiatry," [5] contains many observations which are pertinent here, because they seem to throw light on the pathogenesis of narcolepsy Pavlov found that the intensity of the conditioned reflexes of dogs depended on the intensity of the conditioned stimulus A loud bell produces a greater food excitation than a faint one This is true within certain ranges of the intensity of the conditioned stimulus, but beyond a critical maximal intensity variations of the effect may lead to certain pathologic phases of cortical activity equivalent, in which strong and weak stimuli produce the same effect, paradoxic, in which weak stimuli give a greater response than the strong, or ultraparadoxic, in which excitatory conditioned stimuli become inhibitory and vice versa These excessive stimuli, greater than those required to produce a maximal conditioned response, Pavlov called transmaximal or supramaximal, and these terms were translated by Gantt as ultramaximal Thus, the law may be stated, according to Pavlov's observations, that ultramaximal conditioned stimuli may produce one of three pathologic phases in the cortex of the dog equivalent, paradoxic or ultraparadoxic In his introduction to Pavlov's work, Gantt [6] stated

> In dogs with a "weak nervous system" the above-described phases, particularly the ultraparadoxical, were prominent

Pavlov [7] wrote

> For every one of our animals (dogs) there is a maximum stimulus, a limit of harmless functional strain, beyond which begins the intervention of inhibition (the law of the limit of the intensity of stimulation) A stimulus, the intensity of which is beyond the maximum, instantly elicits inhibition, thus distorting the usual rule of the relationship between the magnitude of the effect and the intensity of excitation

THE "ULTRAMAXIMAL STIMULUS" OF PAVLOV VERSUS THE "EMOTIONAL STIMULUS" OF THE NEUROLOGISTS IN THE PRODUCTION OF CATAPLEXY

The surprising feature of the case reported in the preceding article [8] is the infrequency of cataplectic attacks despite the magnitude and fre-

5 Pavlov, I P Lectures on Conditioned Reflexes, translated by W H Gantt, New York, International Publishers, 1941, vol 2

6 Pavlov,[5] p 14

7 Pavlov,[5] p 51

8 Fabing, H D Narcolepsy I Combat Experience of a Soldier with Narcolepsy, Arch Neurol & Psychiat 54 367-371 (Nov -Dec) 1945

quency of the emotion-laden situations which the soldier had to endure in combat In addition, the case is a lesson It illustrates that cataplexy does not occur in states of great emotional tension but that it is produced by sudden massive stimuli calling for massive response How else can one explain the cataleptic attack produced in an experienced swimmer as a result of diving into water of comfortable temperature, such as occurred in this patient off Bizerte? The sudden massiveness of the cutaneous stimulus (water in contact with the entire surface of the skin) calling for a massive response immediately on rising to the surface (in swimming), and not any emotional quality in the act, produced cataplexy in this patient when he dived into water, both in premilitary and in military life

Sudden laughter, analyzed physiologically, is the result of a massive instantaneous stimulus which calls for a total bodily reaction, and many have experienced the ultramarginal nature of it, with the resulting larval cataplectic phenomenon of motor weakness In the vernacular of the theater there is a current phrase for it—a particularly funny comedy routine "lays the customers out in the aisles" The quick aiming of a gun has the same elements of a massive stimulus, requiring immediate massive motor response, and in my patient, as a consequence, it produced cataplexy whether he was aiming at a rabbit, at quail or at a man The greatest single quality about baseball which makes it an excellent sport for participant and spectator alike is the split second stimulus-response reactions with which it is filled These conditioned reflexes produced a sudden ultraparadoxic phase in my patient, with resultant cataplexy His entire case history can be analyzed and every cataplectic attack can be explained on the basis of a sudden massive stimulus becoming ultramarginal, causing a perversion of the expected motor excitation into sudden motor inhibition Conversely, the failure of cataplexy to occur in many emotion-charged situations, such as the explosion of shells nearby is explained on the basis that the stimuli are not sudden enough in their impact on the central nervous system, and therefore not massive enough, to become ultramaximal As the patient put it, "Shells never bothered me because I could hear them coming, and that way my nerves could get set for them"

It is probably true that no one has ever stopped to inquire into the nature of "emotional" stimuli causing cataplexy One has reckoned only with their affective quality and has not noticed their intensity whereas Pavlov taught that the emphasis should be the other way round Because affect-laden stimuli are usually intense, the mistake is an easy one Wilson suspected it when he wrote that "clinical data, however prove that the matter of surprise has no little to do with cataplectic development" My patient's testimony was more eloquent in its sim-

plicity when he said "It comes on when something big and sudden hits me it's got to be big and fast, though, to knock me down"

One is now in a position to answer some of the questions posed earlier First, what is the peculiar quality of emotional stimuli which produces cataplexy? The answer is that the peculiar quality is the intensity of the emotional stimulus, which in the narcoleptic person, susceptible as he is to excessive inhibition, becomes ultramaximal at lower than normal intensity Second, what is the ill understood reason that emotional stimuli should invariably inhibit motility and tone in cataplectic attacks? In answer, emotional stimuli, being pathologically sudden and intense and therefore ultramaximal, according to Pavlov's law of the limit of the intensity of stimulation, produce the ultraparadoxic phase, with resultant massive inhibition in the motor cortex and consequent cataplectic fall

PAVLOV'S CONCEPT OF INTERNAL INHIBITION, HYPNOSIS AND SLEEP

In the course of his studies on conditioned reflexes in dogs, Pavlov found that excitation could become perverted into inhibition not only by the application of a single massive ultramaximal stimulus but in a second way When an excitatory stimulus of normal intensity is repeated again and again, there is an effect of summation, and this summation of small stimuli gradually transcends the margin, so that the law of the limit of the intensity of stimulation begins to operate once more and perverted states of cortical activity begin to become evident When the ultraparadoxic phase is reached, previously excitatory stimuli, as they impinge on the cortex, become inhibitory The internal inhibition thus generated differs from that produced by a single ultramaximal stimulus In the case of a single ultramaximal stimulus immediate and transient inhibition occurs only in the cells directly involved, whereas in the case of summation of stimuli the slower development of inhibition is accompanied with a tendency of this neural state to spread across the cortex and down the neuraxis

On the basis of these observations, together with many others on inhibition developed by other means, Pavlov came to the conclusion that natural sleep is merely a widespread process of internal inhibition, that it is generated by various means and that it may exhibit many hypnoidal manifestations before complete inhibition occurs He was attracted to the further study of the phenomena "on the brink of sleep," which he found indistinguishable from hypnosis, and he found that many of these partially elaborated hypnoidal states of internal inhibition were analogous to symptoms of neuropsychiatric disorders in man He wrote [7]

> We have seen already how an excitation of the same cell, lasting only a few minutes, lead toward the development in it of a process of inhibition, which

decreases its work and finally stops it altogether Inhibition, as already stated, has a tendency to spread, unless it meets with a counteraction in the conditions of a given environment It expresses itself in phenomena of either partial or total sleep Partial sleep is, evidently, the so-called *hypnosis*

In discussing partial sleep further, he wrote [9]

Irradiation of the inhibitory process of low tension is the condition known as hypnosis and is revealed in conditioned food reflexes by both components, the secretory and the motor When inhibition (either differential or any other kind) arises under the above conditions, it most commonly causes peculiar conditions in the cerebral hemispheres To begin with, contrary to the rule of a normally more or less parallel change in the magnitude of the salivary effect of conditioned food reflexes in accordance with the intensity of the stimuli, all the stimuli are equalised in their effect (the phase of equalisation) Further, weak stimuli produce more saliva than strong ones (paradoxical phase) And, lastly, a perversion of effects occurs the positive conditioned reflex produces no effect whatever, whereas the negative conditioned reflex causes salivation (ultraparadoxical phase) The same is observed as regards the motor reaction, so, when a dog is offered food (*i e*, natural conditioned stimuli are put into action), it turns away from it, while when food is pushed or carried away the dog tries to reach it Besides, it is sometimes possible to observe directly in the condition of hypnosis (in the case of conditioned food reflexes) a gradual spreading of inhibition over the motor region of the cortex The first to be paralysed are the tongue and the muscles of mastication, after which the inhibition of the cervical muscles sets in, and, finally, that of all the muscles of the trunk A further spreading of inhibition down the brain presents sometimes a state of catalepsy and finally manifests itself in heavy sleep

Gantt [10] wrote of these experiments

Also some of these dogs fell into a "hypnotic" state in which there was paralysis of the motor skeletal musculature, especially those muscles most concerned with the given excitation, *i e*, those of eating Such animals stood like marble statues, drooling at the mouth but unable to take food These Pavlov considered analogous to the patients, catatonics, who exhibit catalepsy and remain immobile to even painful stimuli, and consistently refuse food

Thus it is seen that consequent on the spread of inhibition over the hemispheres many of the phenomena seen in the dog under experimental conditions are parallels of those seen in the narcoleptic patient The cataleptic trance state and the sleep paralysis state of the patient are close to the partial sleep state of Pavlov's dogs, who were undergoing the effects of progressive spread of internal inhibition It is evident, too, that the perverted phases of cortical activity, especially the ultraparadoxic, can arise in circumstances other than those produced by excessive or ultramaximal stimuli That the summation of weak submaximal stimuli may, if applied repeatedly, produce inhibition by inducing the ultraparadoxic phase is an experience of everyday life The slight (excitatory)

9 Pavlov,[5] p 174

10 Pavlov,[5] p 14

effect of rain on a tin roof quickly summates by repetition, becomes inhibitory and produces sleep The same may be said for the stimulus of rocking a baby Again the objectivist who watches people in a railway carriage finds that the first part of the journey excites attention, but the summation of the sound of the clickety-click of the wheels, the endless whisking by of telegraph poles through the visual field and the sameness of green fields seen through the window soon produce partial sleep phenomena in most passengers Facial muscles become masklike, eyes stare fixedly ahead, books and newspapers are held in an almost catatonic fashion in the hand Then eyes close, the body sags, the book falls away, and one more traveler is asleep

It appears that the narcoleptic patient differs from the normal person only because his excessive susceptibility to inhibition causes these phenomena to occur at pathologically low thresholds Thus, repetitious stimuli of almost any kind quickly produced the ultraparadoxic phase, with consequent spreading inhibition, in the soldier whose case was described in the previous paper [8] Any monotonous repeated stimulus such as reading a magazine sitting under a tree looking for squirrels or even the whizzing of shells overhead, produced narcoleptic sleep, or partial sleep, in him

It is fair to state, therefore, in answer to the third question posed that by pursuing Pavlov's theory of the spread of internal inhibition as the cause of these states, one may keep in line the apparently divergent phenomena of cataleptic trance, sleep paralysis and actual sleep in a formulation of the pathogenesis of narcolepsy Furthermore, it is evident that these phenomena, like those of cataplexy, are pathologic not in kind but in degree, since larval manifestations are found in normal people In cataleptic trance and in narcolepsy the spread of inhibition is slow and more generalized, whereas in cataplexy the inhibition is sudden and is confined to a group of motor cortical cells destined for excitation but perverted in their activity by a single excessive ultramaximal stimulus In sleep paralysis the two types of inhibition (the slow generalized and the sudden isolated motor type) appear to be combined

ABNORMAL SUSCEPTIBILITY OF THE BRAIN OF THE NARCOLEPTIC PATIENT TO INHIBITION

The pathologic basis of the narcolepsy-cataplexy syndrome, according to the foregoing formulation resides in the abnormal susceptibility of the brain of the patient to inhibition At the present time little is known of the nature of this process The existence of inhibition as a fact of neurophysiology dates from the observation of the brothers Weber a century ago that stimulation of the peripheral end of the cut vagus nerve produces temporary cessation of the heart beat Since

Sherrington's[11] observation, in 1893, that the knee jerk could be inhibited centrally, the phenomenon of inhibition in the central nervous system has been studied extensively The concept of cortical inhibition is not confined to Pavlov Among the more important contributions are those of Dusser de Barenne[12] and his colleagues, who studied the phenomenon of "extinction" in the exposed cortex, which Fulton[13] regards as identical with inhibition Walshe,[14] in a recent analysis of the symptomatology of jacksonian epilepsy, showed the clinical application of spreading, contracting, changing states of inhibition in his cases Pavlov,[15] however, seems to have been the only one to see an answer to the riddle of narcolepsy in this mechanism Although he did not elaborate on his statement, he wrote

> To this mechanism [internal inhibition plus ultraparadoxical phase] one must, I think, refer many pathological symptoms, *e g*, narcolepsy, cataplexy, catalepsy, catatonia, etc

Although the fact of cortical inhibition does not appear to be in dispute, the nature of the phenomenon is not established Gasser[16] stated

> The large number and the diversity of the theories about the nature of inhibition in the nervous system may be taken as a measure of the obscurity which has surrounded the subject Some of the theories are hardly more than restatements in other terms of the fact that the neurons are inhibited Others are fabricated in analogy with conditions making for unresponsiveness in other situations A humoral agent is often postulated, but no such agent has been found, nor is there any evidence for two kinds of fibers, the excitatory and inhibitory, nor for two types of endings for one type of fiber The Wedensky mechanism and anodal polarization are also not infrequently mentioned In every instance, the suggestions can neither be accepted nor rejected

With so little known about the normal process of central inhibition, it is improbable that any satisfying explanation of abnormal susceptibility to the process can be found at this time Pavlov expressed the opinion that the answer to the fundamental nature of inhibition and its pathologic variations would come from the chemists Suffice it to say

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11 Sherrington, C S Note on the Knee-Jerk and the Correlation of Action of Antagonistic Muscles, Proc Roy Soc, London **52**·556-564, 1893

12 Dusser de Barenne, J G, and McCulloch, W S Factors for Facilitation and Extinction in the Central Nervous System, J Neurophysiol **2** 319-355, 1939

13 Fulton, J F Physiology of the Nervous System, ed 2, London, Oxford University Press, 1943

14 Walshe, F M R On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions Beginning Unilaterally" (Jackson), Brain **66** 104-139, 1943

15 Pavlov,[5] p 164

16 Gasser, H F The Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, vol 32, pp 169-193, cited by Fulton,[13] p 85

that the therapy applied today, with success in most cases, is the administration of excitant drugs—drugs which counteract inhibition—namely, ephedrine and amphetamine

The answer to our last question, "What is it about the brain of the narcoleptic patient that makes it so susceptible to inhibition?" cannot be given It can hardly be a static inherent property, for, according to Redlich,[17] the disorder does not ordinarily come on until after puberty A tempting speculation arises if this last fact is considered with Pavlov's observation that the castration of dogs increases inhibition chronically This suggests that the ultimate answer may prove to be an endocrine disorder, but such speculation requires study The failure of autopsy material to aid in understanding the pathogenesis of the disorder is evidently due to the fact that it is a chemical disturbance unaccompanied with structural change

SUMMARY

The case history of a soldier who began to have symptoms of narcolepsy, cataplexy and trancelike catalepsy in 1935 is reviewed His condition was unrecognized, and he went through the Tunisian and Sicilian campaigns of World War II with his disease Attacks of sleep occurred repeatedly throughout his combat career but cataplectic spells were rare, only 2 instances being reported in nine months in the field This absence of cataplectic episodes provoked inquiry into the pathogenesis of the disease, and it was found that cataplexy in man is the result not of an "emotional" stimulus but of an excessively strong, sudden stimulus, which causes a perversion of activity in cortical cells, so that a response destined to be excitatory becomes inhibitory This explanation is found to be consistent with Pavlov's law of the limit of the intensity of stimulation, in which ultramaximal stimuli produce the ultraparadoxic phase in the cortex Further inquiry into Pavlov's theory of sleep indicates that the phenomena of trancelike catalepsy, sleep paralysis and narcoleptic sleep are the result of the spread of inhibition across a brain more susceptible to this state than is the so-called normal brain

CONCLUSIONS

On the basis of analysis of a case of narcolepsy in a combat soldier, a theory of the pathogenesis of narcolepsy, which is essentially an elaboration of the formulation of Wilson, is advanced

1 The brain of the narcoleptic patient is regarded as having an abnormal susceptibility to inhibition, and it is held that this is the fundamental pathophysiologic cause of the disorder

17 Redlich, E Epilegomena zur Narkolepsiefrage, Ztschr f d ges Neurol u Psychiat **136** 128-173, 1932

2 The nature of the process of inhibition in the central nervous system is unknown, and the cause of the abnormal susceptibility of the narcoleptic patient to this process is equally obscure

3 It is held that Pavlov's law of the limit of the intensity of stimulation is applicable to the narcoleptic patient This law states that when a single stimulus or the summated effect of repeated stimuli becomes too strong for the capacity of cortical cells the ultraparadoxic phase of cortical activity supervenes, in which excitatory stimuli become inhibitory

4 In conformity with this law, it is held that the phenomenon of cataplexy results from a single excessive ultramaximal stimulus, the magnitude of which is such that it produces the ultraparadoxic phase and consequent sudden internal inhibition in motor cortical cells which were destined for excitation This sudden inhibition in these cells causes loss of tone and falling to the ground In cataplexy it is held that there is no spread of internal inhibition to cortical fields involving consciousness

5 The case of the combat soldier described here is used to illustrate the fact that it is not the effective quality but, rather, the magnitude of so-called emotional stimuli which provokes the phenomenon

6 The trancelike cataleptic states seen in narcoleptic patients are held to be due to the summation of repeated stimuli provoking the ultraparadoxic phase, with partial spread of internal inhibition to the motor cortical area, producing a partial alteration of movement and plastic tone, or catatonia, without spread to the cortical fields involving consciousness in the usual case

7 The phenomenon of sleep paralysis sometimes seen in narcoleptic attacks is held to be similar to that of cataplexy, but the patient does not fall because he is in the sleeping position at the time It is held that in sleep paralysis there is partial spread of generalized inhibition together with sudden isolated inhibition in motor cortical cells

8 The narcoleptic attack itself is held to be due to the effect of the summation of repeated stimuli, which produce the ultraparadoxic phase, and consequent massive internal inhibition, which spreads widely over the cortex and subcortical centers as well, leading to both the motor and the psychic phenomena of sleep

9 The failure of autopsy material to shed light on this disorder is explained on the basis that abnormal susceptibility to inhibition is probably a chemical disturbance without demonstrable structural change

Conner's Landing, New Richmond, Ohio

DISTURBANCES IN SLEEP MECHANISM
A CLINICOPATHOLOGIC STUDY

V Anatomic and Neurophysiologic Considerations

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ANATOMIC CONSIDERATIONS

FROM the analysis of the material in our previous communications,[1] the cases reported in the literature and the results of animal experimentation, it is possible partly to reconstruct the anatomic centers and their connections regulating the sleeping mechanism

The available data suggest that certain cortical areas, namely, the frontal, premotor, motor, temporal, cingular and hippocampal (as illustrated by the cases in our presentations[1], the cases in Righetti's[2] collection, and the cases reported by Léchelle, Alajouanine and Thévenard,[3] Kolodny,[4] Frazier[5] and others) may act as centers in the integration of hypersomnia and insomnia (figure) The ability of man to fall asleep voluntarily suggests that this mechanism is controlled by

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1 Davison, C, and Demuth, E L Disturbances in Sleep Mechanism A Clinicopathologic Study (*a*) I Lesions at the Cortical Level, Arch Neurol & Psychiat. **53** 399 (June) 1945, (*b*) II Lesions at the Corticodiencephalic Level, ibid **53** 241 (Oct) 1945, (*c*) III Lesions at the Diencephalic Level (Hypothalamus), ibid **55** 111 (Feb) 1946, (*d*) IV Lesions at the Mesencephalo-Metencephalic Level, ibid **55** 126 (Feb) 1946

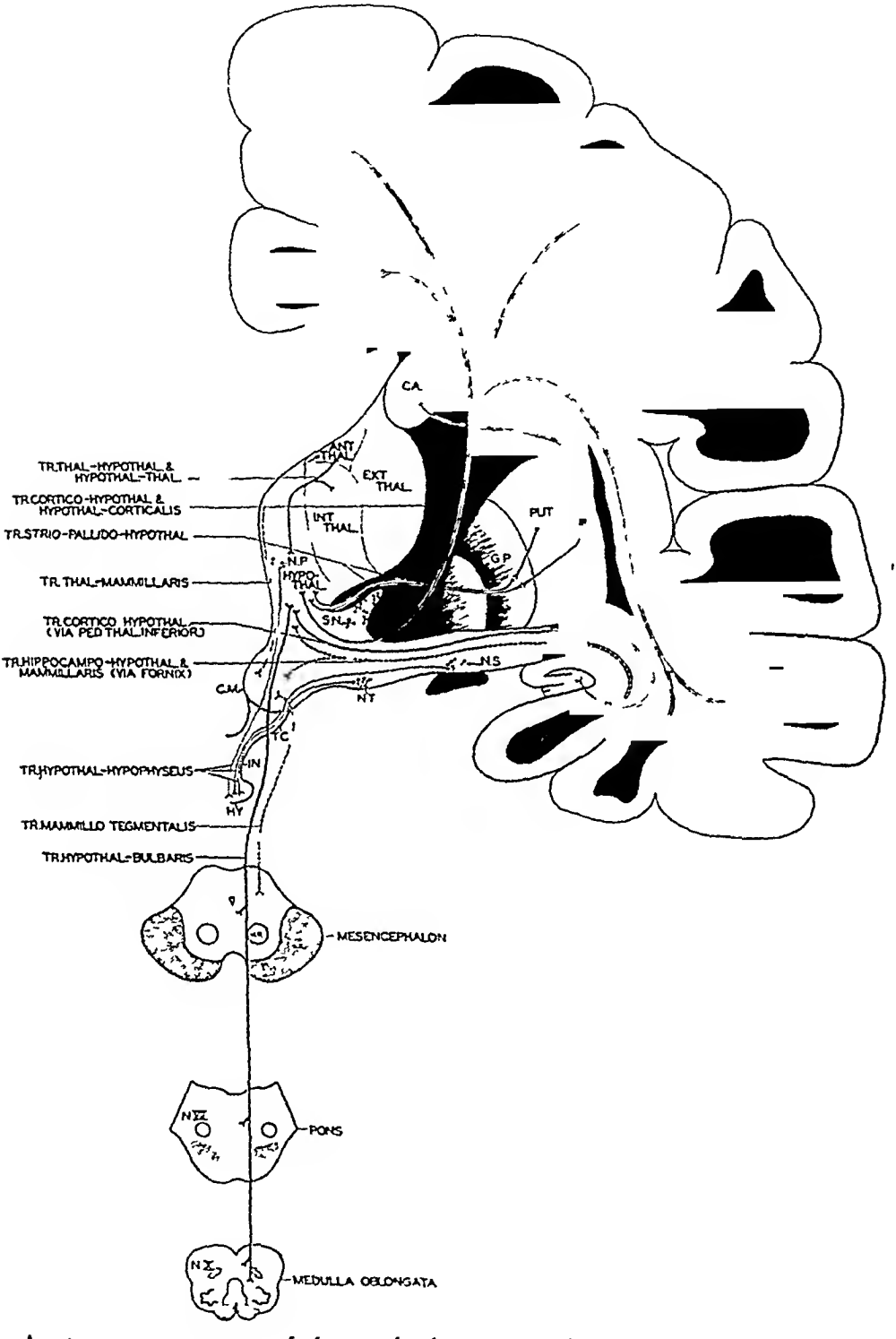
2 Righetti, R Contributo clinico e anatomopatologica allo studio dei gliomi cerebrali e all'anatomia delle vie ottiche centrali, Riv di pat nerv **8** 241 and 289, 1903

3 Lechelle, Alajouanine, and Thevenard Deux cas de tumeur du lobe frontal a forme somnolente, Bull et mem Soc med d hôp de Paris **49** 1347, 1925

4 Kolodny, A The Symptomatology of Tumours of the Temporal Lobe, Brain **51** 385, 1928

5 Frazier, C H Tumor Involving the Frontal Lobe Alone, Arch Neurol & Psychiat **35** 525 (March) 1936

the higher cortical centers Bard's [6] experiments on sham rage furnished further indications that the hypothalamus is to some extent under the



Anatomic connections of the cerebral cortex with centers of the brain stem

6 Bard, P A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am J Physiol 84 490 1928

control of the cerebral cortex Sleep impulses, as in affective states for the expression of emotion and feelings (Davison and Kelman [7] and others), are mediated by voluntary and involuntary pathways, probably controlled by the corticohypothalamic pathways (figure) The voluntary efferent impulses are probably mediated via the pyramidal tract Spiegel [8] and his associates assumed that corticofugal impulses to autonomic structures may be conducted at least partly by fibers joining the pyramidal system and partly by extrapyramidal fibers from areas 3, 4, 5 and 6 Although, according to Spiegel,[8] direct fibers from areas 3 and 5 could not be traced to the hypothalamus, this should not be interpreted as meaning that extrapyramidal conduction of corticofugal impulses from these areas to the hypothalamus does not exist It is possible that the hypothalamus may be reached by extrapyramidal systems using unmyelinated fibers or intercalated relay stations

PROBABLE AFFERENT AND EFFERENT CONNECTIONS OF THE HYPOTHALAMUS

Medial Forebrain Bundle (figure) —This pathway, part of the hippocampohypothalamic tract, consisting of unmyelinated and myelinated fibers, runs between the ventromedial olfactory correlation areas of the cortex and the preoptic and hypothalamic areas and carries both ascending and descending impulses (Ariens Kappers, Huber and Crosby [9], Gurdjian [10], Roussy and Mosinger [11], Fulton and Ingraham,[12] and others) There is a possibility that this bundle is also in intimate connection with the striatum (caudate nucleus and putamen)

Corticohypothalamic Pathways —The cortical control of the hypothalamus is most likely mediated through indirect fiber connection from areas 3, 4, 5 and 6 The only known direct corticohypothalamic

7 Davison, C, and Kelman, H Pathological Laughing and Crying, Arch Neurol & Psychiat **42** 595 (Oct) 1939

8 Spiegel, E A Bemerkungen zur Theorie des Bewusstseins und zum Schlafproblem, Ztschr f d ges exper Med **55** 183, 1927, Die Zentren des autonomen Nervensystems, Berlin, Julius Springer 1928, The Centers of the Vegetative Nervous System, Bull Johns Hopkins Hosp **50** 237, 1932

9 Ariens Kappers, C U, Huber, G C, and Crosby, E C The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936

10 Gurdjian, E S The Diencephalon of the Albino Rat, J Comp Neurol **43** 1, 1927

11 Roussy, G, and Mosinger, M Étude anatomique et physiologique de l'hypothalamus, Rev neurol **1** 848, 1934, L'hypothalamus chez l'homme et chez le chien, ibid **63** 1, 1935

12 Fulton, J F, and Ingraham, F D Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Prechiasmal), J Physiol **67** xxvii, 1929

connections, however, are those of the fornix and certain olfactory systems

The fornix, or the hippocampohypothalamic tract (figure), arising in the hippocampus, is a direct corticohypothalamic pathway As is well known, this pathway contains corticoseptal, corticohabenular and corticohypothalamic fibers The fibers, as demonstrated by Edinger and Wallenberg,[13] end in the medial and lateral mamillary nuclei and in the rostral portion of the tuber adjacent to these nuclei (figure) Papez[14] stated that the fornix is an important link in a circuit controlling the mechanism of emotion

Roussy and Mosinger[11] expressed the belief that fibers from the temporal lobe via the inferior thalamic peduncle (figure) reach the nucleus supraopticus and the anterior hypothalamic area They also mentioned an internal corticohypothalamic fasciculus Greving[15] suggested the existence of a frontotuberal tract Krieg[16] postulated a medial corticohypothalamic tract arising in the hippocampus Nicolesco and Nicolesco[17] stated the belief that cortical fibers reach the hypothalamus via the inferior thalamic peduncle and other paths of the forebrain

The existence of indirect excitatory (Karplus and Kreidl[18]) and inhibitory (Bard,[19] Bard and Rioch[20]) pathways seems to be accepted by many reliable observers (Clark and associates,[21] Ranson and Magoun[22] and others) There also is some evidence for a septohypothalamic pathway, partly by way of the medial forebrain bundle Wallenberg,[23]

13 Edinger, L, and Wallenberg, A Untersuchungen uber den Fornix und das Corpus mammillare, Arch f Psychiat **35** 1, 1902

14 Papez, J W A Proposed Mechanism of Emotion, Arch Neurol & Psychiat **38** 725 (Oct) 1937

15 Greving, R, in von Moellendorff, W Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927

16 Krieg, W J S The Hypothalamus of the Albino Rat, J Comp Neurol **55** 19, 1932

17 Nicolesco, I, and Nicolesco, M Quelques donnees sur les centres vegétatifs de la region infundibulo—tuberienne et de la frontiere diencéphalo-telencéphalique, Rev neurol **36** 289, 1939

18 Karplus, J P, and Kreidl, A Gehirn und Sympathicus II Ein sympathicus-zentrum in Zwischenhirn, Arch f d ges Physiol **135** 401, 1910

19 Bard, P The Central Representation of the Sympathetic Nervous System as Indicated by Certain Physiological Findings, A Research Nerv & Ment Dis, Proc **9** 67-91, 1930

20 Bard, P, and Rioch, D M A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull Johns Hopkins Hosp **60** 73 1937

21 Clark, W E L, Beattie, J, Riddoch, G, and Dott, N M The Hypothalamus, Edinburgh Oliver & Boyd, 1938

22 Ranson, S W and Magoun, H W The Hypothalamus, Ergebn d Physiol **41** 56, 1939

23 Wallenberg A Bemerkenswerte Endstatten der Grosshirnfaserung bei Säugern, Jahrb f Psychiat u Neurol **51** 295, 1934

following frontal lesions in guinea pigs, demonstrated a degenerated neocorticoseptal tract Mettler [24] also showed such a pathway by Marchi preparations in the monkey Clark and associates [21] suggested the existence of a pathway from the frontal lobe to the hypothalamus, with a relay in the zona incerta Possible relays via the dorsal thalamus from the frontal lobe have also been indicated by Clark and associates,[21] Mettler [24] and Levin [25] Our cases of corticodiencephalic lesions [1b] and the reports of other authors also suggest the possibility of such a pathway These cases seem to indicate that the cortex controls the main sleeping center the hypothalamus, either in an excitatory or in an inhibitory manner

Hypothalamocortical Connections—Such pathways have not been demonstrated, but their existence is probable

DIENCEPHALIC AND STRIOPALLIDAL CONNECTIONS

The importance of the hypothalamus, and possibly of other diencephalic structures, in the regulation of sleep has been amply illustrated clinically and experimentally We cannot but strongly emphasize that in many of the clinical cases, including some of our own, the lesions were widespread and postulation of localization on that basis alone should be made with reservations, because areas adjacent to the hypothalamus may also be implicated by compression or edema

Thalamohypothalamic and Hypothalamothalamic Pathways (figure)—These pathways need not be discussed in detail, for the evidence of their existence is generally accepted (Clark and associates,[21] Walker,[26] Crouch and Thompson,[27] Greving [15] and others) Many of the fibers are myelinated Whether these pathways are afferent or efferent systems has not been solved Briefly, it can be stated that they consist of fibers passing from the medial and midline thalamic nuclei to the hypothalamic nuclei (figure) There are also probable connections via the inferior thalamic peduncle with the rostral hypothalamic and the lateral tuberal nuclei In human material, Ingram [28] demonstrated fibers from the anterior part of the thalamus which run ventrally into the medial and lateral preoptic areas Some of these fibers may belong

24 Mettler, F A Corticofugal Fiber Connections of the Cortex of Macaca Mulatta The Frontal Region, J Comp Neurol **61** 509, 1935

25 Levin, P M The Efferent Fibers of the Frontal Lobe of the Monkey, Macaca Mulatta, J Comp Neurol **63** 369, 1936

26 Walker, A E The Primate Thalamus, Chicago, University of Chicago Press, 1938

27 Crouch, R L, and Thompson, J K The Afferent Fibers of the Thalamus of Macacus Rhesus, J Comp Neurol **69** 255 and 449, 1938

28 Ingram, W R Nuclear Organization and Chief Connections of the Primate Hypothalamus, A Research Nerv & Ment Dis, Proc (1939) **20** 195, 1940

to the stria terminalis Farther caudally, fibers appear to swing ventromedially out of the inferior thalamic peduncle into the lateral and anterior hypothalamic regions Many fibers from the substantia innominata enter the lateral preoptic and hypothalamic areas dorsal to the supraoptic nucleus Some fibers from the substantia innominata enter the supraoptic nucleus, turn dorsalward and join the inferior thalamic peduncle, but there is no conclusive evidence that these fibers end in the supraoptic nucleus

Thalamomamillary and Mamillothalamic Fibers—Thalamomamillary connections have been demonstrated in lower forms These fibers set up relays of somatic, visceral and sensory impulses from the neopallium to the hypothalamus The impulses from the hypothalamus to the thalamus are mediated via the (1) mamillothalamic tract (figure), the origin and connections of which are well known and (2) more diffuse and less well defined connections passing through the periventricular system The mamillothalamic tract most likely serves as a link between the hypothalamus and the cerebral cortex, especially the gyrus cingulus Some of the less well defined and diffuse connections belong to the inferior thalamic peduncle, while most of the others lie fairly close to the wall of the ventricle

Stria Terminalis—This also contains preoptic and hypothalamic components, which convey fibers from the amygdaloid nucleus to these regions Ariens Kappers and his associates [9] expressed the belief that fibers of the stria terminalis are distributed to all major hypothalamic areas as far as the perimamillary area, except for the periventricular system and the nucleus suprachiasmaticus, the nucleus paraventricularis and the nucleus supraopticus Roussy and Mosinger [11] and Clark [21] mentioned connections of the stria terminalis with practically all the hypothalamic nuclei In man, Ingram [28] observed fibers of the stria terminalis stream ventrally toward the preoptic and hypothalamic areas, some crossing beneath the anterior commissure

Supraoptic Commissures—These fibers and their relationship to the hypothalamus as afferent systems concerned in the integration of emotional expressions have been emphasized by Papez [14] On the basis of experimental studies in cats, Ingram [28] and his associates stated that they were uncertain whether the specific functions of these commissures had yet been solved

Striopallidohypothalamic and Subthalamohypothalamic Fibers—Such connections have been reported by many observers, but the evidence is not conclusive The secondary involvement of the striatum, pallidum and subthalamic nuclei in many of the clinicopathologic cases and the edema of these structures which must have occurred in the experimental animals suggest that these areas are in intimate connec-

tions with the hypothalamus (figure) Interruption of these pathways on their way to the hypothalamus may lead to disturbances in the sleep mechanism .

EFFERENT SYSTEM

The efferent pathways of this system consist of the following tracts

1 Mamillothalamic tracts

2 Mamillotegmental tract

3 Periventricular system and dorsal longitudinal fasciculus These pathways possibly arise throughout the hypothalamus but come mainly from the posterior hypothalamic area They descend through the central gray matter of the aqueduct, with probable contributions to the tectal and tegmental nuclei (figure)

4 Diffuse descending connections These are caudal continuations of the medial forebrain bundle Physiologic experiments indicate that these fibers are scattered in the lateral portions of the tegmentum and conduct hypothalamic impulses to the lower sympathetic centers

5 Hypothalamohypophysial pathways (figure) This well known tract runs from the supraoptic, paraventricular and tuberal nuclei to the neurohypophysis by way of the neural stalk

6 Intrahypothalamic pathways Of these connections between the various hypothalamic nuclei, the best demonstrated one is that composed of paraventriculosupraoptic and paraventriculotuberal fibers, with unknown destination

7 Fasciculus residualis of Marie and Leri [29] These fibers descend along the optic tract to enter the supraoptic nucleus The fasciculus residualis may belong to the ansa lenticularis

MESENCEPHALOMETENCEPHALOHYPOTHALAMIC SYSTEM

Mamillary Peduncle.—Papez [14] and Rundles and Papez [30] considered this structure as one of the important afferent paths of the hypothalamus Papez [14] suggested that this tract originates from the ventral part of the midbrain and from the substantia nigra He stated the opinion that the substantia nigra, with the medial lemniscus, exercises a dynamic influence on the mamillary body and the mechanism for maintaining general consciousness Ingram [28] expressed the opinion that the mamillary peduncle in man is not very conspicuous and that it is an ascending

29 Marie, P, and Leri, A Persistance d'un faisceau intact dans les bandelettes optiques après atrophie complete des nerfs Le faisceau residuaire de la bandellete, le ganglion optique basal et ses connexions, Rev neurol **13** 492, 1905

30 Rundles, R W, and Papez, J W Connections Between the Striatum and the Substantia Nigra in a Human Brain, Arch Neurol & Psychiat **38** 550 (Sept) 1937

system of mesencephalic origin, ending mostly in the lateral mamillary nucleus He expressed doubt as to whether it contains fibers from the substantia nigra or whether it forms a relay in the lemniscal system

Mamillotegmental Tract—This is the efferent tract, most likely arising from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain (figure) In man, the mamillotegmental tract mingles with descending fibers from other parts of the hypothalamus as it passes into the capsule of the red nucleus

Other Connections—Another efferent connection, demonstrated only physiologically, is the possible vagosupraoptic system (Chang and associates [31], Huang [32], Bronk, Lewy and Larrabee [33]

NEUROPHYSIOLOGIC CONSIDERATIONS

THEORIES OF SLEEP

Numerous theories of sleep have been suggested, and it will be impossible in this presentation to do all of them justice The less important theories will only be mentioned briefly

Humoral Theory—According to some observers, end products of metabolism are accumulated in tissues or in certain organs, resulting in circulatory changes and the induction of sleep The gradual removal of these substances during sleep leads to a return of the waking state Experimental evidence so far has not shown differences in the blood flow in animals during sleep and during wakefulness (Gibbs, Gibbs and Lennox [34]) Another humoral theory is the endocrine, according to which the hypophysis controls the sleep mechanism

Vegetative, or Sympathetic-parasympathetic Theory (Hess [35] and others)—According to Hess,[35] sleep is a parasympathetic function, while waking is the result of action of the sympathetic system

Neural or Dendritic Theories—The main theory of this type states that the dendrites of the cortical cells are retracted by ameboid movements, thus breaking the contact with neighboring neurons and resulting

31 Chang, H C, Hsieh, W M, Li, T H, and Lim, R K S Humoral Transmission of Nerve Impulses at Central Synapses IV Liberation of Acetylcholine into the Cerebrospinal Fluid by Afferent Vagus, Chinese J Physiol **13** 153, 1938

32 Huang, J J A Vagus-Post-Pituitary Reflex IV On the Determination of Its Pathways with a Comment on the Hypothalamic Sympathetic Mechanism, Chinese J Physiol **13** 367, 1938

33 Bronk, D W, Lewy, F H, and Larrabee, M G The Hypothalamic Control of Sympathetic Rhythms, Am J Physiol **116** 15, 1936

34 Gibbs, F A, Gibbs, E L, and Lennox, W G The Cerebral Blood Flow During Sleep in Man, Brain **58** 44, 1935

35 Hess, W R Der Schlaf, Klin Wchnschr **12** 129, 1933

in sleep Powerful impulses leading to elongation of the dendrites reestablish the broken contacts and result in awakening

Inhibition Theories—Of inhibition theories advocated by several investigators, the only one discussed here is that proposed by Pavlov [36] According to this investigator,[36] sleep is the result of a widespread cortical inhibition Inhibition is the decrease in activity of one part of an organ as a result of excitation or increased activity elsewhere Pavlov stated the belief that sleep is nothing but internal inhibition which is widely radiated, extending over the whole mass of the cerebral hemispheres and involving the lower centers of the brain as well The inhibition thus can not only affect the entire cerebral cortex but can extend to subcortical areas This widespread radiation of cortical inhibition is a result of conditioned stimuli, the repeated application of which leads to sleep Experimental observations by others (Liddell, Anderson and James [37]) failed to support the summation and radiation theories of internal inhibition

Narcoleptic sleep, according to Wilson,[38] cannot be explained on the basis of this theory, for the patient sometimes is asleep on his feet while walking, marching or on horseback—a state which cannot be identified with cortical inhibition alone Pavlov's theory underrates the comparative anatomy of the diencephalic center, the existence of which experimental and clinicopathologic studies confirm

Corticodiencephalic and Diencephalic Theories (Purkinje and associates,[39] Mauthner,[40] Kleitman [41] and others) —The corticodiencephalic, or evolutionary, theory presupposes that for the initiation of sleep there is an interruption of the afferent pathways to the cerebral cortex As a result of pathologic changes in the ventricular gray matter (Mauthner [40]), there occurs a break in the conducting pathways to and from the cerebral cortex Afferent stimulation does not reach consciousness, and efferent impulses do not reach the hypothalamus because of a break in conduction in the central gray matter despite the fact that the sensory and motor cortex may be intact There is suggestive experi-

36 Pavlov, I P The Identity of Inhibition with Sleep and Hypnosis, Scient. Monthly **17** 603, 1923 Innere Hemmung der bedingten Reize und der Schlaf, ein und derselbe Prozess, Skandinav Arch f Physiol **44** 42, 1923

37 Liddell, H S , Anderson, O D , and James, W T An Examination of Pavlov's Theory of Internal Inhibition, Am J Physiol **90** 430, 1929

38 Wilson, S A K The Narcolepsies, Brain **51** 63, 1928

39 Purkinje, J E Wachen, Schlaf, Traum und verwandte Zustande, in Wagner, R Handworterbuch der Physiologie, Brunschweig, F Vieweg u Sohn, 1846, vol 3, p 412

40 Mauthner, L Pathologie und Physiologie des Schlafes, Wien klin Wchnschr **3** 445, 1890

41 Kleitman, N Sleep and Wakefulness as Alternating Phases in the Cycle of Existence, Chicago, University of Chicago Press, 1939

mental evidence (Bremer [42] and Adrian [43]) that in normal sleep the cortex becomes deafferented, and, therefore, that sleep is impossible without the cortex According to this theory, wakefulness is a subcortical, most likely a hypothalamic, function, whereas forced wakefulness and diurnal sleep are cortical functions Ranson [44] called forced wakefulness, or wakefulness of necessity, a hypothalamic drive The failure to keep the center for wakefulness (hypothalamus) in a state of continued excitation causes a return to the condition of sleep At this point it may be advisable to review briefly the experimental data showing the important role that the diencephalic centers, especially the hypothalamus, play in the regulation of the sleep function For the data regarding the influence of the cerebral cortex on sleep or wakefulness, the reader is referred to the discussion in previous publications [1] on lesions at the cortical and corticodiencephalic levels

PHYSIOLOGIC EVIDENCE

Experimental Lesions—Experimental lesions in the region of the hypothalamus are variable and numerous Most of the experiments (Marinesco, Sager and Kreindler [45], Ito [46], Ranson and Ingram,[47] and Barris and Ingram [48]), especially those by Ranson and his co-workers, which were controlled very carefully, prove that the hypothalamus is concerned with the mechanism of sleep Ranson [49] and his associates found that damage to the posterior part of the lateral hypothalamic area bilaterally produced somnolence Somnolence could be induced in animals in which the central gray matter around the aqueduct was spared, and it was not present in some animals with lesions of the central gray matter around the aqueduct Destruction of the anterior part of the lateral hypothalamus was less effective in producing somnolence than destruction of the posterior part In 7 monkeys large bilateral lesions in the thalamus did not produce somnolence Ranson [49] con-

42 Bremer, F Cerveau "isole" et physiologie du sommeil, Compt rend Soc de biol **118** 1235, 1935

43 Adrian, E D The Physiology of Sleep, Lancet **1** 1296, 1937

44 Ranson, S W The Hypothalamus Tr & Stud, Coll Physicians, Philadelphia **2** 222, 1934, Sleep, Scient Monthly **38** 473, 1934

45 Marinesco, G, Sager, O, and Kreindler, A Recherches expérimentales sur le mecanisme du sommeil, Bull Acad de med, Paris **100** 752, 1928

46 Ito, S Das Tuber cinereum und der Schlaf, Fukuoka-Ikwadaigaku-Zasshi **24** 35, 1931, abstracted, Ber u d ges Physiol u exper Pharmakol **64** 156, 1932

47 Ranson, S W, and Ingram, W R Catalepsy Caused by Lesions Between the Mammillary Bodies and Third Nerve in the Cat, Am J Physiol **101**:690, 1932

48 Barris, R W, and Ingram, W R The Effect of Experimental Hypothalamic Lesions upon Blood Sugar, Am J Physiol **114** 555, 1936

49 Ranson, S W Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch Neurol & Psychiat **41** 1 (Jan) 1939

cluded that the posterior part of the lateral hypothalamic area is the center for integration of emotional expression and suggested that it be termed a waking center When it is thrown out of function, somnolence ensues Harrison [50] (1940), by placing bilateral electrolytic lesions in the lateral hypothalamic area, produced somnolence Clinically, in most of our cases of somnolence with lesions of the diencephalon the posterior and lateral parts of the hypothalamus were involved Because other parts of the hypothalamus were also involved, it would be impossible, on a clinicopathologic basis, to state definitely that only the posterolateral part of the hypothalamus is concerned with somnolence

Electrical Stimulation.—Electrical stimulation of the diencephalon in animals was carried out by Marinesco and associates [45], Ito [46], Hess [35], Mussen [51], Kabat, Anson, Magoun and Ranson [52], Wassermann,[53] and and Harrison [50] In none of these experiments was sleep produced, but most observers elicited evidences of excitement White [54] found that in man mechanical and electrical stimulation of the hypothalamus produced bradycardia, a rise in blood pressure and a tendency to drowsiness or coma Hess [35] was the only one who induced sleep by stimulation of structures in the brain stem His results were accepted by many observers (von Economo,[55] Ebbecke,[56] Adie,[57] Tromner [58] and others) as proving Pavlov's [36] contention that sleep is an active inhibition of the cortex Hess's [35] experiments were justifiably criticized by Harrison, Magoun and Ranson,[59] who repeated the experiment

50 Harrison, F An Attempt to Produce Sleep by Diencephalic Stimulation, J Neurophysiol **3** 156, 1940, Hypothalamus and Sleep, A Research Nerv & Ment Dis, Proc (1939) **20** 635, 1940

51 Mussen, A T Cerebellum and Red Nucleus, Arch Neurol & Psychiat **31** 110 (Jan) 1934

52 Kabat, H, Anson, B J, Magoun, H W, and Ranson, S W Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am J Physiol **112** 214, 1935

53 Wassermann, M Prispevik, therapii nespavosti, Časop lek česk **63** 273, 1924, abstracted, Med Klin **20** 1018, 1924

54 White, J C Autonomic Discharge from Stimulation of the Hypothalamus in Man, A Research Nerv & Ment Dis, Proc (1939) **20** 854, 1940

55 von Economo, C Ueber den Schlaf, Wien klin Wchnschr (supp) **38** 1, 1926, Studien uber den Schlaf, Wien med Wchnschr **76** 91, 1926, Schlaftheorie, Ergebn d Physiol **28** 312, 1929

56 Ebbecke, U Physiologie des Schlafes, in Bethe, A, and others Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol 17, p 563

57 Adie, W J Idiopathic Narcolepsy A Disease Sui Generis, with Remarks on the Mechanism of Sleep, Brain **49** 257, 1926

58 Tromner, E Funktion und Lokalization des Schlafes, Arch f Psychiat **86** 184, 1929

They showed that sleep was easily obtained by passage of the current through the lateral hypothalamic area, but only when such stimulation was associated with corresponding lesions Many animals which gave evidence of excitement and did not go to sleep showed no lesions microscopically In many animals with sleep disturbances the lesions were small and could easily have been overlooked by a method of localization such as the vertical projection technic used by Hess [35] Harrison [50] also produced somnolence in several animals by passing a steady direct current through the lateral hypothalamic area, lesions were present in these animals Gagel [60] noticed sleep and unconsciousness in 14 cases in which the caudal part of the hypothalamus was mechanically stimulated at operation He stated the belief that the caudal part of the hypothalamus is inhibitory to the cortex, whereas the oral part is excitatory Damage to the oral part, according to Gagel,[60] results in decreased cortical activity The consensus seems to be that when sleep is caused by passage of an electric current it is the destructive effects of the current and not the stimulating factors which are responsible for the somnolence

PHARMACOLOGIC EVIDENCE

Barbiturates—Some observers concluded that the hypothalamus was the sleep center because they demonstrated a selective concentration of barbiturates in the hypothalamus during narcosis (Sahlgren,[61] Lafora and Sanz [62]), while others indicated that barbiturates are present in high concentration in the hypothalamus during anesthesia (Keeser and Keeser [63]) These assumptions have been refuted by Koppanyi, Dille and Krop [64] and others

Sympathomimetic and Parasympathomimetic Drugs and Their Antagonists—Cannon's [65] concept of the parasympathetic system as

59 Harrison, F , Magoun, H W , and Ranson, S W Some Determinations of Thresholds to Stimulation with the Faradic and Direct Current in the Brain Stem, Am J Physiol **121** 708, 1938

60 Gagel, O Symptomatologie der Erkrankungen des Hypothalamus, in Bumke, O , and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 5, p 482

61 Sahlgren, E Experimentelle Untersuchungen uber den Angriffspunkt des Luminals im Gehirn bei Kaninchen, Acta psychiat et neurol **9** 129, 1934

62 Lafora, G R , and Sanz, J Sul sonno sperimentale prodotto da una azione su la regione del diencefalo e del III ventricolo, Cervello **11** 86, 1932

63 Keeser, E , and Keeser, J Ueber die Lokalisation des Veronals, der Phenylathyl- und Diallylbarbitursaure im Gehirn, Arch f exper Path u Pharmakol **125** 251, 1927

64 Koppanyi, T , Dille, J M , and Krop, A Studies on Barbiturates VII Distribution of Barbiturates in The Brain, J Pharmacol & Exper Therap **52** 121, 1935

65 Cannon, W B , and Rosenblueth, A Autonomic Neuro-Effector Systems, New York, The Macmillan Company, 1937

preserving the bodily reserves suggested to some observers that sleep is essentially a parasympathetic integration As is well known, during normal sleep various divisions of the parasympathetic outflow are active This is manifested by constriction of the pupils, slowness in heart action and retardation of the oxidation processes in the body as a whole Some investigators have attempted to produce sleep with drugs known to stimulate structures innervated by the sympathetic nervous system Marinesco, Sager and Kreindler,[66] on the basis of the production of a delayed sleeplike state in animals by the intraventricular injection of choline, a parasympathetic stimulant, suggested the possibility of a parasympathetic dominance during sleep Dikshit,[67] by injecting acetylcholine into the lateral ventricles or directly into the hypothalamic region in cats, produced a condition closely resembling sleep Henderson and Wilson,[68] however, were unable to produce sleep in most of their patients In these subjects the slight effects of the acetylcholine were abolished by atropine It was therefore concluded that the action of acetylcholine is central and that there is no conclusive evidence that acetylcholine or choline can produce sleep by central stimulation of parasympathetic centers Harrison[50] Hess[69], Marinesco, Sager and Kreindler,[66] and Lafora and Sanz[62] produced sleep with intraventricular injections of ergotamine They expressed the belief that this action was due to a depression of the central sympathetic centers, with dominance of the parasympathetic system The effect of ephedrine, which alleviates somnolence in cases of narcolepsy, was thought to indicate that the drug increases the activity of the central sympathetic centers Ranson and Magoun[22] concluded that the parasympathetic dominance was probably due to decreased sympathetic, and not to parasympathetic, activity So far there is insufficient evidence that sleep is the result of increased parasympathetic activity

Chemical Stimulation—Metallic Ions It is known that an increase in the concentration of ionic calcium causes a decrease in the irritability of neural tissue, whereas an increase in the concentration of ionic potassium increases the irritability Demole[70] and Cloetta and

66 Marinesco, G, Sager, O, and Kreindler, A Experimentelle Untersuchungen zum Problem des Schlafmechanismus, Ztschr f d ges Neurol u Psychiat **119** 277, 1929

67 Dikshit, B B Action of Acetylcholine on the "Sleep Centre," J Physiol **83** 42P, 1934

68 Henderson, V E, and Wilson, S C Intraventricular Injection of Acetylcholine and Eserine in Man, Quart J Exper Physiol **26** 83, 1936

69 Hess, W R Ueber die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen, Schweiz Arch f Neurol u Psychiat **15** 260, 1934

70 Demole, V Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch f exper Path u Pharmakol **120** 229, 1927

Fischer [71] injected small amounts of Ringer solution, containing calcium chloride, into the region of the infundibulum of rabbits and cats and produced a state resembling normal sleep Marinesco, Sager and Kreindler [66], Lafora and Sanz,[62] and others produced sleep by intraventricular injections of calcium and elicited excitement, sometimes followed by delayed sleep, with potassium salts Brunelli [72] found that certain ionic metals produce sleep, in the following order of efficacy calcium, barium, strontium, magnesium, lithium, sodium and potassium Cloetta and Fischer [71] reported that there was an increase in the calcium concentration of the hypothalamus during narcosis This observation, and the fact that the blood calcium falls during narcosis and sleep, led them to conclude that sleep is brought about by a shift of calcium from the blood to body tissues, including the hypothalamus Katzenelbogen,[73] however, found no such increase of calcium in the brain during sleep, and Cooperman [74] disclosed that the fall in blood calcium during sleep occurs after the beginning of sleep and is coincident with bodily relaxation According to Harrison,[50] there is no possible way to interpret the results of injections of calcium as phenomena of stimulation or excitation Pharmacologically, it can be stated that there is insufficient evidence that the hypothalamus acts as a sleep center

PSYCHOLOGIC CONSIDERATIONS

Normal sleep is essentially a biologic function, governed chiefly by the hypothalamus The fact that man is able to fall asleep consciously or unconsciously on attempting to escape certain emotional difficulties or to keep awake voluntarily in emergency situations or under deep emotional strain would indicate that the higher cortical centers also play an important role in the regulation of sleep and in their influence on the hypothalamus Examples of higher cortical influences on the regulation of sleep are numerous and were discussed in detail in another presentation (Davison [75]) It is also well to bear

71 Cloetta, M, and Fischer, H Ueber die Wirkung der Kationen Ca, Mg, Sr, Ba, K und Na bei intrazerebraler Injektion (Beitrag zur Genese von Schlaf und Erregung), Arch f exper Path u Pharmakol **158** 254, 1930

72 Brunelli, B Contributo alla fisiopatologia dei centre vegetativi del diencefalo con speciale riguardo al centro per la regolazione de sonuo e della veglia, Riv biol **14** 375, 1932

73 Katzenelbogen, S The Distribution of Calcium Between Blood and Cerebrospinal Fluid in Sleep Induced by Diallyl-Barbituric Acid, Arch Neurol & Psychiat **37**·154, 1932

74 Cooperman, N R Calcium and Protein Changes in Serum During Sleep and Rest Without Sleep, Am J Physiol **116**·531, 1936

75 Davison, C Psychological and Psychodynamic Aspects of Disturbances in Sleep Mechanism, Psychoanalyt Quart **14** 478 (Oct) 1945

in mind that cortical activity does not cease during sleep Discoveries have been synthesized in sleep and dreams

The hypothalamus, the main and most important vegetative center, plays a part not only in the control of water and carbohydrate metabolism, the maintenance of normal sleep rhythms and the stabilization of body temperature and cardiac, respiratory and gastrointestinal functions, but in the mechanism producing such emotions as fear, anxiety and anger The hypothalamus is undoubtedly part of the motor mechanism through which emotional states are expressed The influence of acute emotions on bodily functions is generally accepted today It is needless to repeat the general bodily, and especially visceral, responses, including sleep, which may result from emotional disturbances, such as fear, anxiety, rages or unconscious repressed drives

Until recently, it was thought that the state of sleep constituted merely a diminution or lessening in the general biologic activities of the organism The act of sleeping, however, must also be considered as a fundamental psychobiologic protective function against physical and mental exhaustion, operating as a means of helping the person to keep up his instinctual equilibrium Sleep, in other words, is a nightly regression, associated with a temporary denial of reality and apparent blocking of certain motor activities Sleep or somnolent states and insomnia may thus assume the character of a psychophysiologic defense mechanism against dangerous collisions between the individual's drives and the surrounding world hostile to his instinctual demands Sleep is a temporary, narcissistic withdrawal of the ego, or, as Freud [76] put it, a reenacting of the life in utero by refusing consciously to perceive stimuli from the external world If one accepts the theories of unconsciousness, repression and regression and the freudian interpretation of dreams, it follows that sleep disturbances (insomnia and somnolence) occurring in the psychoneuroses, in twilight states and somnambulism (Davison [75]) and even in some organic diseases with psychoneurotic manifestations are retreats in order to avoid the unpleasant features of reality, the powerful and perverted instinctual drives In other words, in sleep the person wishes to lose contact with the outer world and with reality In some cases of somnolence the retreat is resorted to in order to obtain gratification—a wish fulfilment of the distorted instinctual drives

As already indicated, every emotional situation is invariably associated with some physiologic response, such as sweating, palpitation, shortness of breath, pallor, blushing, changes in blood pressure, erection of hair, sphincteric disturbances, laughter, weeping and sleeplessness or somnolence These physiologic responses take place when the

76 Freud, S Collected Papers, London, Hogart Press, 1933

emotional causes of the psychologic conflict cannot be expressed and released through normal voluntary channels, i e, they are repressed These physiologic responses are undoubtedly mediated and controlled by the cortex, by the hypothalamus, and possibly by other subcortical structures The repressed drives, such as sexual conflicts, hostility or guilt feelings, lead to chronic emotional tensions, which, in turn, result in dysfunction of the vegetative nervous system, with subsequent disturbances in digestion, respiration, circulation and sleep It is impossible to understand or to study these emotional conflicts and their early influence on bodily changes, including sleep, with the present laboratory technical methods They have to be approached through psychologic studies

SUMMARY AND CONCLUSIONS

From the analysis of the clinicopathologic material presented, the cases reported in the literature and animal experiments, it is possible to reconstruct the centers and pathways concerned with the sleep mechanism

The cases of cortical lesions indicate that fibers for the control of sleep may originate in the cerebral cortex, especially the hippocampal, cingular, frontal, premotor and temporal convolutions To a certain extent, therefore, the hypothalamus is under cortical control These impulses are mediated by voluntary and involuntary pathways The main afferent and efferent pathways connecting the hypothalamus and the cortex are (1) the medial forebrain bundle, which runs between the ventromedial olfactory correlation areas of the cortex and the preoptic and hypothalamic areas, and (2) the corticohypothalamic pathways which are essentially the fornix and the inferior thalamic peduncle The connection furnished by the latter fibers between the cortex and the hypothalamus is best illustrated by the cases of corticodiencephalic lesions Other, less well established, corticohypothalamic pathways are the frontotuberal tract and the neocorticoseptal tract There are experimental suggestions that in normal sleep the cortex becomes deafferented Sleep, therefore, is impossible without the cortex Forced wakefulness and diurnal sleep are cortical functions

The evidence in the clinicopathologic cases of the diencephalic group and the results of other anatomophysiologic investigations indicate that the hypothalamus is the main center regulating sleep The hypothalamus is in intimate connection with the thalamus, the striopallidum and the hypophysis, and its main afferent and efferent pathways are as follows

1 Thalamohypothalamic and hypothalamothalamic pathways They consist essentially of fibers from the medial and midline thalamic nuclei to the hypothalamic nuclei

2 Thalamomamillary fibers These pathways set up relays of somatic, visceral and sensory impulses from the neopallidum to the hypothalamus The impulses from the hypothalamus to the thalamus are mediated via the mamillothalamic tract

3 Mamillotegmental tract This tract consists of fibers from the mamillary bodies terminating in the tegmentum

4 Stria terminalis This structure, which also contains preoptic and hypothalamic components, conveys fibers from the amygdaloid nucleus to the hypothalamus

5 Supraoptic commissure

6 Striopallidohypothalamic and subthalamohypothalamic pathways The existence of such connections, reported by many observers, has not been fully accepted

7 Hypothalamohypophysial pathways These fibers run from the supraoptic, paraventricular and tuber nuclei to the neurohypophysis

8 Interhypothalamic pathways These fibers connect the various hypothalamic nuclei

Lesions interrupting these pathways may lead to sleep disturbances Some of our clinical material and the results of animal experimentation indicate that bilateral damage to the posterior part of the lateral hypothalamic area produces somnolence When the waking center, the hypothalamus, is disturbed, somnolence ensues The secondary involvement of the thalamic nuclei, striatum and pallidum in many of the clinicopathologic cases and the edema of these structures in the experimental animal suggest that these areas may also be concerned with regulation of sleep Their influence, however, is mostly the result of involvement of the pathways which are in intimate association with the hypothalamus

There is some evidence, largely clinical, that somnolence or other disturbances in the sleep mechanism may result from lesions at the mesencephalometencephalic level These lesions were usually in the region of the periaqueductal gray matter The known hypothalamic and mesencephalometencephalic connections are via (1) the mamillary peduncle, probably an ascending system of mesencephalic origin ending mostly in the lateral mamillary nucleus, and (2) mamillotegmental tract, an efferent pathway arising most likely from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain

The opinion that somnolence and lethargy are related to lesions in the nuclei of the ocular nerves cannot be accepted, for these phenomena were essentially observed in the cases of the mesencephalometencephalic group and in some of the cases of the diencephalic group The absence of such dysfunction in the other groups and the lack of sleep distur-

bances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism

Psychologic consideration of psychogenic disturbances and of some organic disorders with psychoneurotic symptoms indicates that the pathways and centers aforementioned, especially the hypothalamus, are important in the regulation of sleep In most of the cases of psychogenic disorders sleep is a retreat in order to avoid the unpleasant features of reality, the powerful and perverted instinctual drives In some cases of somnolence the retreat is resorted to in order to obtain gratification—a wish fulfilment of the distorted instinctual drives The repressed drives lead to emotional tensions, which, in turn, result in dysfunction of the vegetative nervous system, of which sleep forms a part

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EXTENSIVE EROSION OF THE BASE OF THE SKULL FROM A LEPTOMENINGEAL CYST

Report of a Case

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AND
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MEDICAL CORPS, ARMY OF THE UNITED STATES

EROSION of the cranial bones from pressure of a leptomeningeal cyst is an uncommon, but not rare, condition While the majority of such cysts develop after severe trauma to the skull, usually with fracture, there is evidence that congenital abnormalities in the dura and leptomeninges may contribute to their production Haymaker and Foster [1] reported a case in which a large collection of clear, colorless fluid resembling cerebrospinal fluid was found enclosed between the two layers of the dura in the posterior cranial fossa, a small defect was present beneath the tentorium, through which a lobule of the cerebellum was herniated While their patient gave a history of a fracture of the skull in childhood, the separation of the dural layers and the small subtentorial defect may have been congenital abnormalities which favored development of a cyst in this location

Leptomeningeal cysts have been noted more commonly in the parietal, frontal and occipital regions In the case to be described a difficult diagnostic and therapeutic problem was presented by the presence of an extensive area of destruction of bone in the floor of the middle cranial fossa

REPORT OF CASE

A 28 year old soldier was admitted to an Army general hospital with swelling about the right orbit and temporozygomatic region and with exophthalmos on the same side One and one-half years before, in North Africa, the patient had received a mild cerebral concussion as a result of an explosion of several large bombs The following morning he noticed swelling of the right temple and slight exophthalmos These symptoms persisted for several days and then disappeared, but he continued to have occasional dull, aching pains in the right orbital region, which were relieved by analgesics One year later he had pneumonia and was hospitalized It was then noted that there were slight swelling of the temple and slight exophthalmos on the right side, with slight constriction of the right pupil No other abnormal physical or neurologic signs were present Roentgenographic examination of the skull revealed a group of cystic-appearing shadows in the right anterior temporal region and in the superior, posterior and lateral

1 Haymaker, W, and Foster, M E, Jr Intracranial Dural Cyst, with Report of a Case, J Neurosurg 1 211-217, 1944

walls of the right orbit with thinning of bone in these regions It was thought that the patient had an expanding cystic tumor of bone, or possibly a vascular neoplasm Because of the apparent rapidity of growth, he was evacuated by air to the United States

Examination—On admission to an Army general hospital, the patient was entirely asymptomatic Examination showed pronounced exophthalmos of the right eye and bulging of the entire right temporozygomatic region without discoloration The swelling was moderately firm, nontender and slightly pulsatile The margins were ill defined, but the swelling appeared to be limited below by the zygomatic arch and lateral wall of the maxilla There were no palpable nodes in the neck or the preauricular region Extraocular movements were normal, and there was

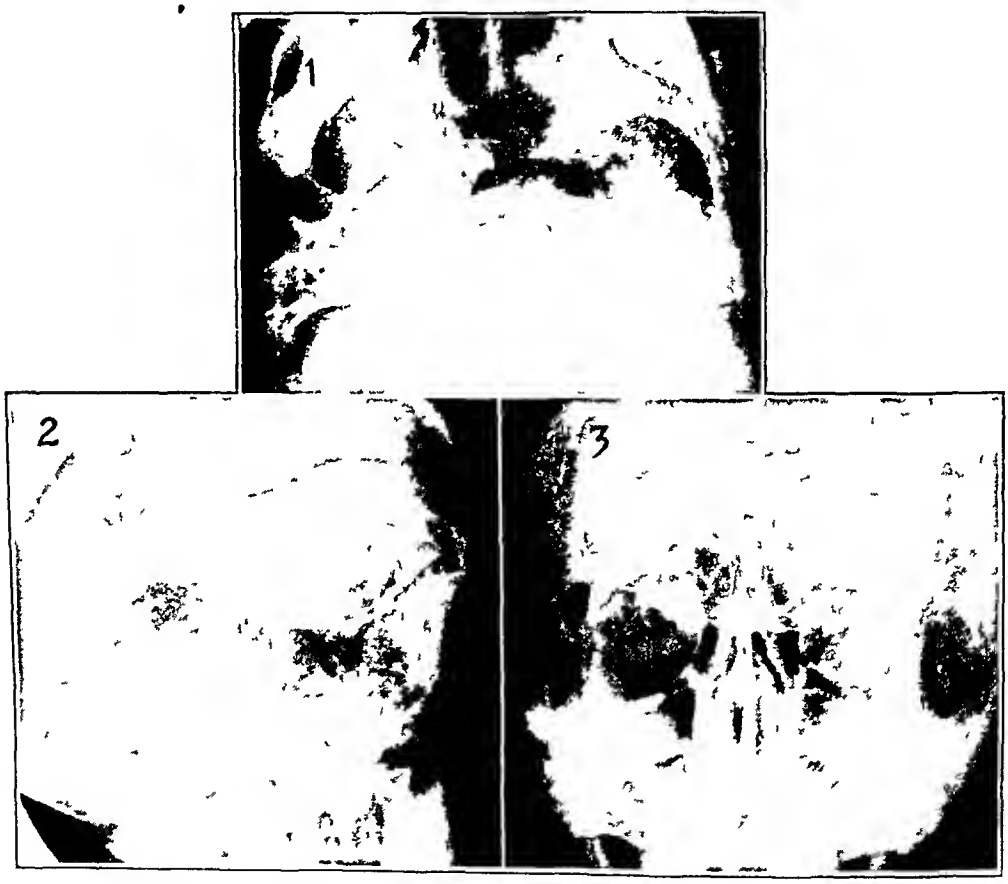

Fig 1—*1,* verticosubmental projection, demonstrating erosion of the sphenoid bone on the right An expansile mass crosses the midline *2,* oblique projection of the orbit, revealing erosion of the sphenoid bone behind the lateral rim of the orbit *3,* posteroanterior projection, demonstrating erosion of the greater and lesser wings of the sphenoid bone on the right

no increasse in intraocular tension Vision was 20/20 in each eye and the visual fields and fundi were normal The remainder of the physical examination was noncontributory

Roentgenographic examination of the skull revealed an extensive destructive lesion involving almost all the greater wing of the sphenoid bone on the right, the more lateral portion of the lesser wing and the body of the sphenoid bone behind the sphenoid sinus, where it crossed the midline (fig 1*1*) There was visible erosion of the walls of the foramen lacerum medium, the foramen ovale and the foramen spinosum on the right There was also extension across the

sphenotemporal suture into the more anterior part of the squamous portion of the temporal bone While the process was almost wholly osteolytic, at the margins in several places a fine line of density demarcated the lesion from the adjacent normal bone There was no evidence of increased vascular markings in the skull near the lesion, and no other abnormalities were noted The sella turcica and the paranasal sinuses were of normal appearance Conventional posteroanterior and lateral roentgenograms were less informative than stereoscopic projections of the base (verticosubmental, fig 1 *1*) and of the orbits (optic canal position, fig 1 *2*)

Pneumoencephalographic studies showed normal distribution of gas in the ventricles and the basal cisterns No gas was noted in the subarachnoid space about either temporal lobe There was no evidence of dilatation, asymmetry or displacement of the ventricles

Laboratory studies revealed nothing abnormal

Differential Diagnosis—A number of conditions were considered in the diagnosis, some of which were ruled out, for obvious reasons

1 Meningioma While there was extensive involvement of the sphenoid bone, the ridge appeared to be intact, and there was no evidence of hyperostosis of the ridge or of the olfactory groove The absence of abnormality revealed by the cerebral air study offered additional evidence against this diagnosis

2 Epidermoid Tumors or Cholesteatoma The majority of such tumors which have acquired the large size of the lesion noted in this case present dense, irregular borders, and the bone within shows patchy erosion with islands of noneroded bone remaining, thus giving a mottled, or honeycomb, appearance However, in rare cases there may be complete loss of bony structure It was felt, therefore, that the diagnosis of such a tumor could not be excluded

3 Osteogenic Sarcoma A tumor of the osteolytic type is rare in this location, the extension of the process across the sphenotemporal suture and the fine line of density demarcating the margins of the lesion were evidence against this diagnosis

4 Xanthomatoses (including eosinophilic granuloma) While single cranial lesions are less common than multiple, the roentgenographic appearance may be similar to that noted in this case The characteristic finding is that of a punched-out lesion with sharply outlined margins It was felt that the diagnosis of such a lesion could not be excluded

5 Leptomeningeal Cyst The history of previous trauma to the skull followed by destructive change in the bone is suggestive, the location is unusual While thinning, bulging and central erosion of bone are noted commonly over a cyst, there is rarely complete loss of bone over a wide area It was believed that the diagnosis of such a lesion was possible but not probable

6 Myeloma Solitary myelomas are found occasionally in the skull, but rarely do they acquire the size noted in this case without secondary or accompanying lesions elsewhere Moreover, they are more likely to occur in older people

7 Metastatic Malignant Disease The absence of multiple lesions offered evidence against the diagnosis of this condition

8 Localized Osteitis Fibrosa Cystica In reported cases there is expansion of the diploe with thinning, but not destruction, of the inner and outer tables It was believed that the diagnosis of such a condition could be excluded

Operative Observations—With endotracheal anesthesia, a hidden frontotemporal incision was made When the temporalis muscle was incised and reflected, a membrane was found to bulge through a large area of erosion in the greater

wing of the sphenoid bone and the anterior margin of the squamous portion of the temporal bone A needle was inserted through the membrane, and about 10 cc of clear, watery fluid was aspirated This white, thick-walled cyst appeared to be extracranial, but by continued exploration it was found that this was only a small locule of a larger, thin-walled cyst, which was apparently covered by dura The lateral wall of the right orbit was found to be paper thin, mobile and displaced inward by an extension of this cystic mass It was then found that this larger cystic mass extended downward along the base of the middle cranial fossa, with complete loss of bony structure downward and forward as far as the pterygoid fossa anteriorly, the body of the sphenoid bone medially and the styloid process of the temporal bone posteriorly The gasserian ganglion and the maxillary and mandibular nerves were exposed, and the cystic mass was dissected from them The temporal lobe of the brain was exposed at its tip, where there were some adhesions to the meninges about the neck of the large sac Small hemostatic clips were inserted to show the limits of the dissection (fig 2) The large cavity occupied by the cyst was filled with fibrin foam in thrombin, and fascia from the

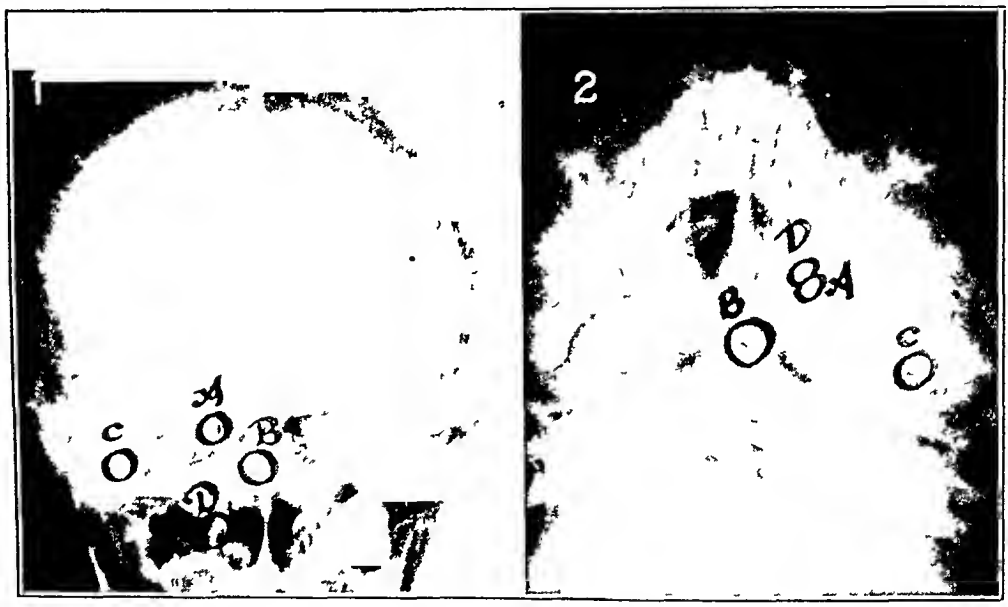

Fig 2—*1,* posteroanterior projection (postoperative), showing hemostatic clips at the margins of the area of operative exploration *A* is placed at the junction of the body and the right greater wing of the sphenoid bone, *B,* within the body of the sphenoid bone, behind and below the sphenoid sinus, *C,* in the most posterolateral portion of the lesion, lateral to the temporal lobe, and *D,* in the most inferior portion of the lesion, behind the right pterygoid process *2,* vertigosubmental projection (postoperative)

temporalis muscle was used to repair the dural defect The wound was closed, using interrupted sutures in the temporalis muscle and the skin

Examination of fluid removed from one of the cysts revealed 1 leukocyte per cubic millimeter, 15 mg of sugar and 217 mg of total protein per hundred cubic centimeters, a strongly positive reaction for globulin and 600 erythrocytes per cubic millimeter

Microscopic sections of the membrane of the cyst showed a thin fibrocollagenous wall lined with flattened cells There was a well vascularized fibroblastic zone incorporating hyaloid and collagenous foci, which probably represented villous processes arising from the wall The histopathologic picture suggested that the

tissue was dura mater and neomembrane which had undergone collagenous degeneration

Postoperative Course.—The patient made an uneventful recovery except for paralysis of the right lateral rectus muscle and resultant diplopia, both of which disappeared within two months

COMMENT

Collections of fluid, clear or xanthochromic, within the subarachnoid or subdural space or between layers of the dura have been noted after trauma and occasionally as sequelae of meningoencephalitis. The mechanics of production is not thoroughly understood, however, it is probable that as a result of injury or infection arachnoid granulations develop, with production of adhesions. If these adhesions are so disposed as to close off a portion of the subarachnoid space, it is believed that one or more cysts may form. Leptomeningeal cysts have been reported as occurring in practically all portions of the subarachnoid space, including the basal cisterns, the space over the cerebral and cerebellar hemispheres and even within the cortical sulci. At times, because of size and location they may produce clinical effects similar to those noted with neoplasms.

According to Dyke,[2] the cysts which follow trauma to the skull are more apt to result from severe injuries especially comminuted and depressed fractures with extensive damage to the leptomeninges. Months or years later there may be clinical evidence of a meningeal cyst at the site of injury, with thinning and bulging of the bone over the cyst and frequently persistence or actual widening of the original fracture line. The inner table of the skull is usually eroded with production of a scalloped effect near the margins of the cyst. Rarely, as in the case reported here, there are complete erosion of both tables and bulging of the cyst into the pericranial soft tissues. About the margins of the lesion there may be evidence of hypervascularity of the bone.

Schwartz[3] called attention to a lesion which is noted in occasional cases—the presence of irregular areas of thickening of the bone of the inner table over a cyst. He expressed the belief that these areas are due either to the healing of an antecedent fracture or to an atypical reaction of the bone to the underlying cyst.

Some leptomeningeal cysts produce no recognizable change in the cranial bones. If such a lesion is suspected, pneumoencephalographic studies may be of assistance in identification and localization.

2. Dyke, C. G.: The Roentgen-Ray Diagnosis of Diseases of the Skull and Intracranial Contents, in Golden, R.: Diagnostic Roentgenology, New York, Thos. Nelson & Sons, 1941, chap. 1, pp. 302-331.

3. Schwartz, C. W.: Leptomeningeal Cysts from a Roentgenological Standpoint, Am. J. Roentgenol. **46**: 160-165, 1941.

It is of interest in this case that the entire cyst appeared to lie completely outside the cranial cavity, owing to the extensive area of erosion of bone It may be that much of the pressure erosion came from without, after the cyst had once herniated through the floor of the middle cranial fossa This fact is probably responsible for the absence of symptoms and neurologic signs

SUMMARY

A case of leptomeningeal cyst of the right middle cranial fossa, following injury one and one-half years before operation, is reported

The unusual feature of the case was the extensive destruction of bone in the middle cranial fossa, with complete erosion of both tables of the skull and herniation of the cyst into the pericranial tissues

PAROXYSMAL AUTONOMIC CRISES IN THE POSTENCEPHALITIC STATE

Report of a Case

CHARLES I OLLER, M D
PHILADELPHIA

PAROXYSMAL autonomic crises or attacks as a manifestation in the postencephalitic state have not been described in standard neurologic textbooks Reports of this syndrome in the literature have been exceedingly rare in spite of the voluminous material on the sequelae of epidemic encephalitis Consequently when one is confronted with the striking group of symptoms that constitute the autonomic crisis in postencephalitic patients, many apparently new and troublesome questions present themselves For this reason the following unusual case is reported

REPORT OF CASE

The patient, a 41 year old Negro, had a high school education and was rather intelligent The family history was noncontributory In 1918, at the age of 15 he had a severe bout of "influenza" and in the following year he exhibited behavior difficulties, necessitating his remaining away from school for about a year In 1923, at the age of 20, he had an attack or a relapse of encephalitis, during which he remained unconscious for thirty-six hours In subsequent years there was progressive development of the defects of paralysis agitans with locomotor and speech troubles In addition he exhibited various antisocial trends and behavior complications He served several terms in jail for a number of misdemeanors and finally received, in 1939 a six to nine year sentence for attempted rape of a woman who kept house for him

During the three years prior to his admission to the state hospital, while he was still in prison, the patient became subject to peculiar attacks, which became progressively more frequent and more intense These attacks were described by the prison medical authorities as temper tantrums or outbursts of violence and by the patient himself as "spells of cramps in the legs and hollering" These attacks finally became so severe that the patient was transferred to the Philadelphia General Hospital, in September 1944, for possible commitment to an institution for the insane

On the fifth day after his admission to the Philadelphia General Hospital he suddenly became agitated, excited and noisy It was noted by the resident that he had tonic contractions of the muscles and that he sweated profusely His pulse was recorded as 140 per minute and his temperature as 101 F In two hours the pulse rate and temperature were back to normal, and the patient returned to

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From the Philadelphia State Hospital and the Department of Neurology University of Pennsylvania Graduate School of Medicine

This case was reported at a meeting of the Philadelphia Neurological Society, April 27, 1945

his previous state of composure The physician in charge expressed the opinion that this peculiar episode was an anaphylactic reaction to 10 drops of tincture of stramonium given a few minutes previously and set about proving his point by administering minute doses of the drug However, there was no further recurrence, and the patient was transferred to the Philadelphia State Hospital on Oct 16, 1944

On admission he presented a picture of advanced paralysis agitans, with the typical facies, posture, gait, slowness of muscular response and rigidity There were, however, essentially no tremors except those of the tongue and mouth when he attempted to speak Speech was impaired by interminable trembling stuttering and repetitiousness to the extent that it was difficult to understand him The pupils were unequal, the right being about 3 mm and the left 2 mm in diameter They did not react to light or in accommodation Convergence was poor, and there was vertical nystagmus on both upward and downward gaze Otherwise, the neurologic examination showed an essentially normal condition He weighed 131

Fig 1 —Patient as he appeared on admission to the Philadelphia State Hospital

pounds (59 4 Kg) and showed considerable emaciation There was drooling of saliva from the mouth, and the face was greasy with excessive sebaceous secretion The blood pressure was 100 systolic and 60 diastolic, the pulse rate was 80, and the temperature and respiration were normal No other abnormal signs were noted He was mentally clear and alert, but conversation could be carried on only with great difficulty because of his speech troubles

The urine was normal The blood urea measured 11 mg and the blood sugar 70 mg per hundred cubic centimeters, and the Wassermann reaction of the blood was negative The spinal fluid was clear and under normal pressure and contained no cells the Wassermann reaction was negative, and the colloidal gold curve was normal Roentgenograms of the skull and the chest were normal

About two weeks after his admission he had the first of the many episodes which came under my observation These attacks occurred on the average of

perhaps once a week They differed somewhat in intensity, so that they could be described as light or severe The majority were severe A description of a typical attack follows

The patient becomes restless and begins to groan The groaning grows louder, shriller and more frequent, occurring more or less synchronously with expiration, until it resembles the barking of a dog When questioned at this stage he points to his legs and cries, "Cramps in the legs, cramps in the legs, cramps in the legs"! Within one-half hour to an hour the legs are extremely rigid and hyperextended, so that at times the body is lifted from the bed, resting on the heels and shoulders There are rapid trembling of the entire body, especially the legs, and a peculiar flapping of the forearms and hands, and in general he shows extreme agitation, so that it is necessary to use physical restraint Respiration by this time is panting and reaches a rapidity of 60 or more per minute The body is drenched in profuse perspiration, and the sheets of the bed not only are soaked but gather pools of moisture The pulse rate is 160 per minute, and the temperature (rectal) at its height is 106 5 F The blood pressure is 80 systolic

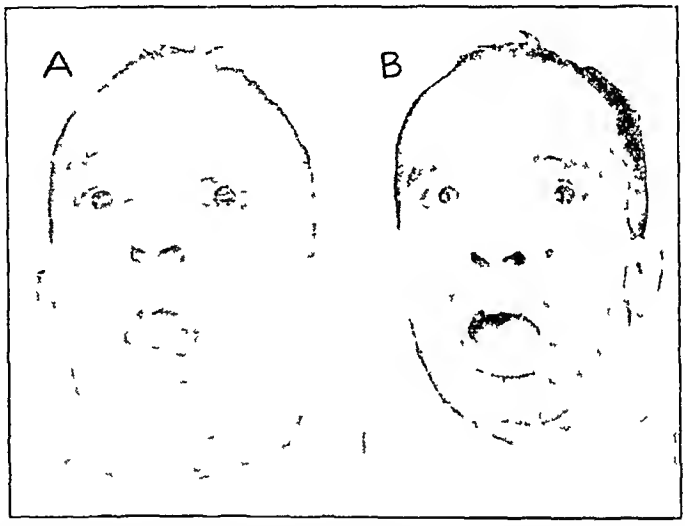

Fig 2—*A*, patient during an autonomic attack Note the bulging eyes, panting nostrils and dripping streaks of perspiration *B*, patient in another autonomic paroxysm

and 40 diastolic The face looks wild, presenting an expression between panic and rage The eyeballs protrude, and the pupils are widely dilated He strikes at every one approaching him All these symptoms reach their peak in three or four hours and abate in six to eight hours Subsequently the patient is exhausted quiet and sleepy Later still he is back to his usual status He apologizes to any one whom he may have struck during his peculiar outburst He cannot explain why he should strike any one He has an excellent recollection of all that has taken place He describes his spell as an attack of cramps in the legs (Figs 2 and 3)

The foregoing description is that of a severe, but fairly typical, episode There were variations, however, particularly as regards intensity and duration Mild attacks had a duration of only one or two hours, and one very severe episode lasted about twenty-four hours There were mild episodes in which the chief symptoms were muscular rigidity and cramps, with no significant changes in respiration, pulse or temperature The highest recorded temperature was 106 7 F

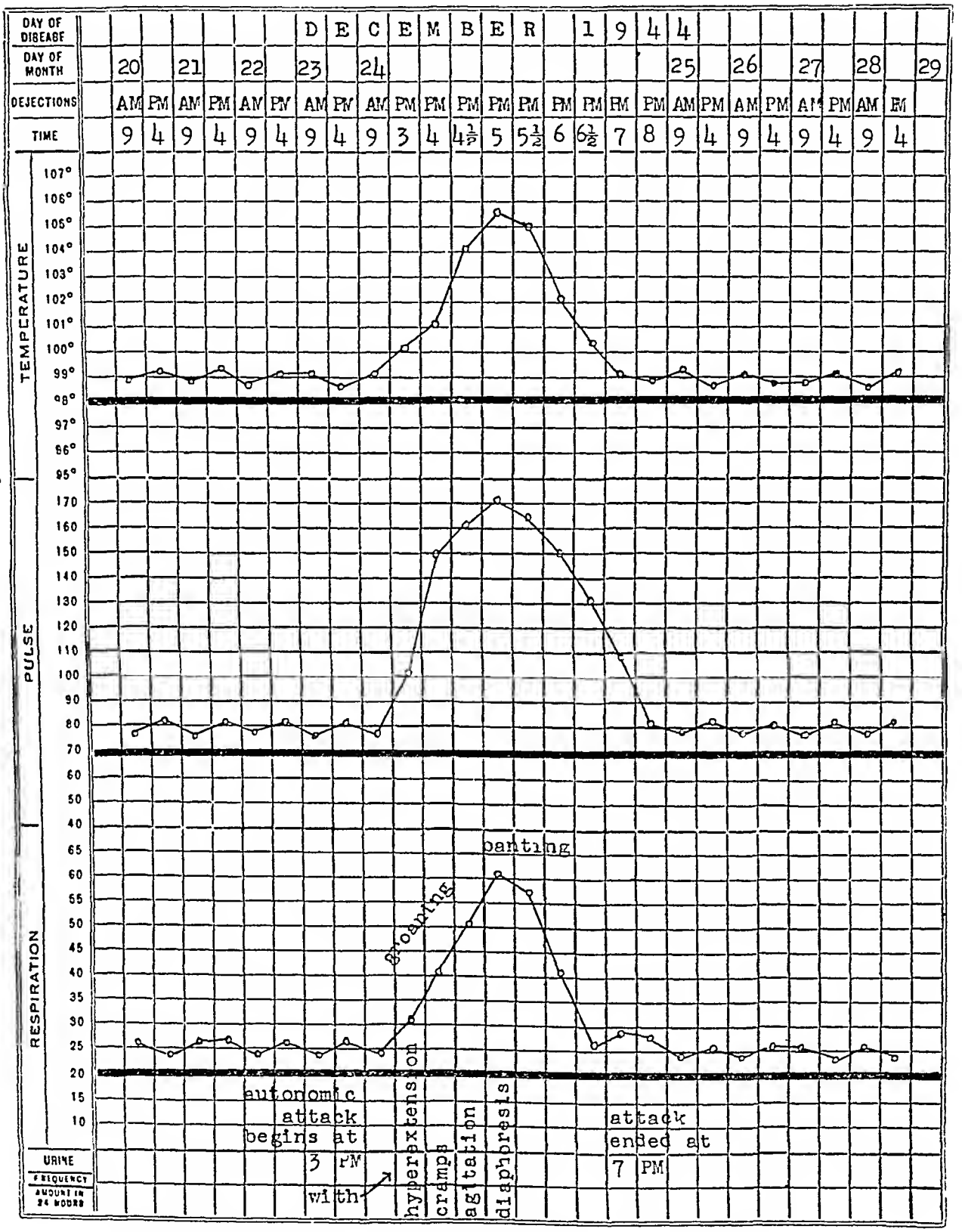

Fig 3—Chart showing the respiration, pulse and temperature curves during a paroxysm

Usually, however, the elevation was to 104, 103 or even 101 F In one attack, while the temperature did not exceed 101 F, the pulse rate rose to 180 and the respiratory rate to over 60 per minute The frequency of attacks was also variable, so that at their oftenest these episodes occurred every two or three days Usually, however, they were a week apart, and the longest interval between attacks was fourteen days

It should be added that interspersed between the attacks, and bearing no relation to them, there were occasional mild oculogyric spasms, which were, however, so slight that they attracted no attention

Laboratory studies made during a severe paroxysm revealed 4,370,000 red blood cells, 13 Gm of hemoglobin per hundred cubic centimeters and 9,600 white cells, with 67 per cent polymorphonuclear leukocytes The blood sugar measured 202 mg per hundred cubic centimeters The spinal fluid was clear and under a low pressure of 50 mm of water It contained no cells The total protein of the fluid measured 29 mg, the sugar 38 mg and the chlorides 650 mg, per hundred cubic centimeters A roentgenogram of the chest again showed nothing abnormal, and

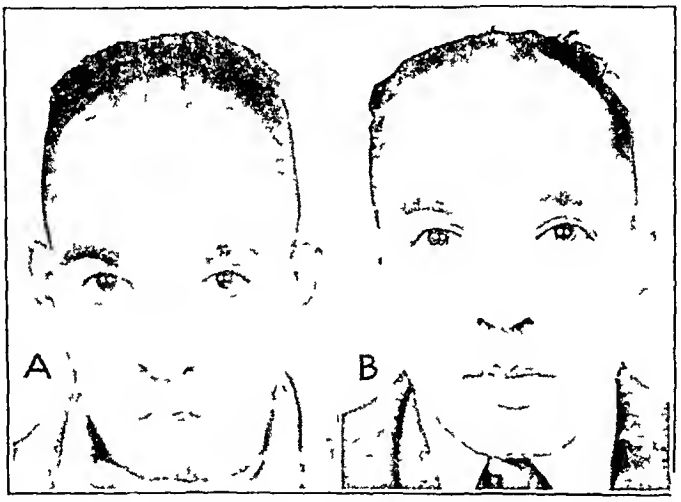

Fig 4—*A*, patient about two months after he was placed on scopolamine therapy, *B*, patient as he appeared at the time of writing

neither clinical nor roentgenographic examination revealed any enlargement of the liver or spleen A painstaking examination of several specimens of the blood, taken at the height of fever, revealed no malarial organisms Agglutination tests were negative for typhoid, relapsing fever and infection with Brucella abortus

It is to be noted that this patient, in spite of the advanced symptoms of paralysis agitans present for many years, had not received any of the routine drug treatments He was kept without drugs for a considerable period while at this hospital for purposes of observation It was during this period that he had his most severe episodes During the attacks he was given various types of treatment, including subcutaneous injections of caffeine and sodium benzoate and of morphine sulfate and intravenous injections of atropine sulfate and of sodium amytal None of these drugs had any beneficial effect The sodium amytal definitely aggravated the attack Its injection resulted in considerable coughing and bronchial secretion and delay in the return of the temperature and pulse to normal It was finally noted that injection of 1/75 grain (0 8 mg) of

scopolamine hydrobromide terminated the episode within one-half to one hour This drug was subsequently resorted to for control of the attacks The patient was ultimately placed on regulation treatment consisting of oral administration of scopolamine hydrobromide, 1/75 grains three times a day

He was observed for a period of two months while receiving treatment and for a similar period while without treatment During the period of the treatment he had five attacks, all of which were relatively mild and of short duration During the two months in which he was without treatment he had ten attacks, most of which were severe Moreover, between attacks he was rather feeble, could scarcely walk and spent a great deal of time in bed, whereas with treatment he was ambulatory, cheerful and helpful about the ward (fig 4 *A*)

COMMENT

The phenomenon of crises of the autonomic system in the postencephalitic state is so little known that when it does occur it presents considerable difficulty in diagnosis and interpretation Thus, the episodes exhibited in the case reported here were considered by the medical authorities of the prison hospital as psychically induced temper tantrums, while a resident at a general hospital suspected that he was dealing with a drug sensitivity Another physician, impressed by the paroxysms of high temperature, considered a diagnosis of malaria likely The course of events and a more thorough investigation made the true character of the symptoms apparent The phenomena displayed during the attacks can be subdivided physiologically into a group involving the vital autonomic functions, including tachycardia, tachypnea, diaphoresis and hyperthermia, a group expressing emotional release, resembling "sham" rage, and a group concerned with manifestations of muscular release, including pronounced rigidity, hyperextension, tremors and agitation

The role of the diencephalon, in particular the hypothalamic region, as the center of the autonomic and emotional functions has been adequately established by the experimental work of Bard,[1] Ranson, Cannon,[2] Cushing[3] and others Paroxysmal autonomic release phenomena as a clinical manifestation was first reported by Penfield[4] in a patient who was found to have a tumor involving the diencephalon Paroxysmal autonomic episodes in the postencephalitic state have previously been

1 Bard, P The Hypothalamus and Sexual Behavior, A Research Nerv & Ment Dis, Proc (1939) **20** 551, 1940

2 Cannon, W B The Wisdom of the Body, ed 2, New York, W W Norton & Company, Inc, 1939, Bodily Changes in Pain, Hunger, Fear and Rage, New York, D Appleton-Century Company, 1915

3 Cushing, H Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill, Charles C Thomas, Publisher, 1932

4 Penfield, W Diencephalic Autonomic Epilepsy, Arch Neurol & Psychiat **22** 358 (Aug) 1929

reported in only 3 or 4 instances. Wimmer,[5] of the Copenhagen clinic, in his monograph on the sequelae of epidemic encephalitis, described a case in which paroxysmal episodes of agitation and muscular spasms were associated with excessive perspiration, tachypnea and rapid, regular pulse, but with no rise in temperature. Neal,[6] in her volume on encephalitis lethargica, sponsored by the Mathison Commission, in which she summarized the work on hundreds of cases of encephalitis, did not mention this syndrome at all but did refer to the well known fact that there are autonomic disturbances in the postencephalitic state. Borremans and van Bogaert[7] reported 2 clear cut cases of paroxysmal vegetative syndromes associated with postencephalitis which, in the essentials, resembled the case here reported, as well as Penfield's case. In 1 of their cases autopsy revealed characteristic changes in the substantia nigra, as well as peculiar, Alzheimer-like changes throughout the diencephalon, from the region of the thalamus to the oculomotor nucleus. In 1943 Ostow[8] reported a case of a patient with postencephalitis who had attacks in which, in addition to cataleptic manifestations, such as akinesia, rigidity and mutism, he exhibited autonomic reactions, consisting of diaphoresis, rapid pulse (110 to 140 a minute), fever (100.6 F.) and hypertension. It must therefore be concluded that diencephalic paroxysms in their extreme form constitute a relatively rare occurrence in the postencephalitic state. Indeed, during a period of over five years of almost daily observation of, and close contact with, about 100 patients with paralysis agitans in various stages of advancement, I have not come across another case of similar attacks, although oculogyric crises were commonplace. It might be that in a mild form these episodes go unnoticed. It should also be noted that this patient, although having had postencephalitis for about twenty years, had had no previous routine drug therapy, and this may have had something to do with the occurrence of the attacks. As a matter of fact, the episodes were greatly reduced in intensity and frequency on the institution of regular treatment with scopolamine. The pathophysiology of the syndrome cannot be discussed here except to point out that this syndrome is another example of the numerous episodic manifestations that are common in this disease, as witnessed by oculogyric spasms, cataplexy,

5 Wimmer, A. Further Studies upon Chronic Epidemic Encephalitis, London, William Heinemann, Ltd., 1929.

6 Neal, J. B. and others. Encephalitis. A Clinical Study. New York, Grune & Stratton, Inc., 1942.

7 Borremans, P., and van Bogaert, L. Paroxysmal Vegetative Syndromes of Central Origin. Two Cases, Presse med. **44**: 1091 (July 4) 1936.

8 Ostow, M. Recurrent Autonomic Phenomena Associated with Exacerbations of Postencephalitic Parkinsonism. Report of a Case, Arch. Neurol. & Psychiat. **50**: 342 (Sept.) 1943.

narcolepsy, hyperkinetic attacks, tonic fits, temporary psychoses, hallucinations, compulsions and emotional outbursts

SUMMARY

A case of paroxysmal autonomic crises occurring in a patient with postencephalitis is reported The attacks consisted in the sudden appearance of extreme tachycardia, tachypnea, hyperthermia and diaphoresis, associated with emotional manifestations resembling "sham" rage and with pronounced muscular hypertonic phenomena Some of the difficulties and errors of diagnosis are discussed A survey of the literature reveals that this syndrome is a rare sequel of the postencephalitic state The attacks could be partially controlled by the subcutaneous administration of 1/75 grain (0 8 mg) of scopolamine hydrobromide and were considerably reduced in intensity and severity by regular scopolamine therapy

NOTE —The preceding report covered the period of the patient's progress up to March 15, 1945 On April 27, 1945, the case was presented before the Philadelphia Neurological Society The following report is a summary of what has happened to the patient since

On March 15, 1945, treatment was changed to include amphetamine sulfate, 10 mg , twice a day, in addition to the usual administration of 1/75 grain of scopolamine hydrobromide three times a day The patient has been on this regimen up to the time of writing, Sept 15, 1945 During this period of six months he has had one major autonomic crisis, which occurred on April 26 He has had none since There have been instead minor attacks of a sort which do not differ much from the spells commonly seen in other patients with encephalitis and which do not attract any particular attention They last about one-half to one hour and consist primarily of an exacerbation of rigidity with or without oculogyric phenomena They occur infrequently, on an average of about once a month

The patient has otherwise done well He has gained about 40 pounds (18 Kg), now weighing 170 pounds (77 1 Kg) He is comfortable, up and about and helpful with ward work He still shows the usual neurologic picture of severe paralysis agitans, his speech particularly being greatly affected, but there are essentially no tremors

It seems, therefore, that his present therapeutic regimen, consisting in the combined use of large doses of scopolamine and amphetamine, is effective in eliminating or reducing to insignificance his previous autonomic paroxysms, which were of such severity that each one of them threatened to terminate his life The efficacy of this combination for the control of severe symptoms, especially of a paroxysmal nature, in patients with postencephalitis is thereby reaffirmed

DISCUSSION

DR BERNARD J ALPERS One feature of this case interested me particularly I wonder whether this man actually showed rage during the course of the outbursts Was it rage, or was it a reaction of pain to the cramps in his legs? It looks as though it might have been the latter In other respects the case resembles very much that of diencephalic epilepsy described by Penfield

I have seen what seem to be two types of diencephalitis in children One was that of a girl addicted to phenobarbital who had a typical syndrome of this sort, with changes in sweating, pulse and temperature during the course of her attacks These symptoms disappeared when she recovered, and several months later she had had no more of the episodes

DR CHARLES RUPP JR I wonder whether Dr Oller attempted to precipitate any of these attacks by administering drugs intravenously or intramuscularly I recall several years ago giving epinephrine intravenously to an extremely depressed patient in order to investigate the hysterical manic attacks, which were somewhat similar to those Dr Oller described and the patient went into a manic-like episode for a short period

DR FRANCIS M FORSTER I should like to ask whether Dr Oller had an opportunity to get an electroencephalogram during one of these spells

DR CHARLES I OLLER The main reason for presenting this case was to bring to attention a striking, though rare, manifestation in the postencephalitic state namely, autonomic fits

With regard to Dr Alpers's question whether there was actually an element of rage or whether the patient's behavior was mere expression of pain, one has as evidence, in addition to the facial expression, which of course is not specific, the fact that the patient would strike at all those about him, without any reason after which he was always sorry

I was not interested in precipitating any attacks with the use of sympathicotonic drugs, since I was more anxious to terminate them when they occurred, inasmuch as the patient was often deathly sick with them

No electroencephalographic study was made as it did not seem to me that the results would contribute to an understanding of the case

Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Physiology and Biochemistry

INHIBITION OF ACTIVITY IN SINGLE AUDITORY NERVE FIBERS BY ACOUSTIC STIMULATION ROBERT GALAMBOS and HALLOWELL DAVIS, J Neurophysiol **7** 287 (Sept) 1944

Galambos and Davis studied by means of microelectrodes the nerve impulses in a single auditory nerve fiber The spontaneous discharges which occur in silence in some fibers can be stopped by certain tones or noises Inhibitory and excitatory tones for each fiber fall into a definite range of frequencies, but there is no common relation between fibers as to the relationship of these inhibitory and excitatory frequency ranges The discharge excited by an adequate tone also can be reduced or abolished by the simultaneous presentation of a second tone, when the inhibitory areas may encroach on and overlap the response area The inhibitory action of low tones on activity aroused by high tones is more widespread than the inhibitory influence exerted by high tones over the excitatory action elicited by low tones The mechanism of the inhibition is unknown Factors referable to the middle and inner ear have been excluded The authors suggest that nerve fibers underlying the organ of Corti play a role The function of the inhibition is obscure, but it seems probable that it plays a role in the phenomenon of masking

FORSTER, Philadelphia

INFLUENCE OF CONDITIONING NERVE STIMULI ON RELAYED VOLLEYS EVOKED FROM SPINAL CORD PERIODIC FACILITATION AND INHIBITION CARL GUSTAF BERNHARD, J Neurophysiol **7** 397 (Nov) 1944

Bernhard stimulated locally by means of electrodes placed laterally in the spinal cord and elicited a number of oscillations of synchronized impulses in the peroneal nerve The various synchronized waves of this complex response could be inhibited or facilitated by conditioning stimuli administered to the ipsilateral popliteal nerve, depending on the time interval between the conditioning and the test stimulus The conditioning stimulus administered to the popliteal nerve produced a rapid periodic variation of inhibition and facilitation, with four inhibitory minimums and four excitatory maximums The number of depressions and facilitations may vary from experiment to experiment, but the temporal location with reference to the conditioning stimulus is constant

FORSTER, Philadelphia

EYE MOVEMENTS IN ELECTRICAL SHOCK PROCEDURE F F KINO, J Ment Sc **90** 592 (April) 1944

Kino found that patients subjected to electric shock therapy always showed lateral deviation of the eyes in the same direction Usually there was faint homonymous deviation of the head, but some patients kept the head turned straight forward or turned it to the opposite side The number of patients deviating the eyes to the left was about equal to the number deviating to the right Right or left handedness has no bearing on the direction of deviation, nor does age, sex or character of the mental disturbance

The direction of deviation of the eyes could be reversed in many patients by having them fix their gaze in the direction desired for two or three minutes before shock was given A few failed to show deviation of the eyes to either side after this effort Many showed deviation similar to that they had presented before,

i e, without previous fixation of gaze Other workers had shown that stimulation of one or the other frontal adverse visual fields would produce conjugate deviation to the opposite side The observations presented by Kino showing bilateral response after bilateral simultaneous stimulation led him to conclude that since the deviation is always the same in a given case its direction cannot be due to external factors but must be inherent in the physiology of the subject, it must be based on a difference in degree or duration of a sustained excitation in both adversive visual fields The effect of conscious inhibition on one visual field prior to shock is in keeping with this observation

McCarter, Boston

Experimental Edema of the Brain II Factors Which Influence the Edema S Obrador Alcalde and J Pi-Suñer, Bol d Lab de estud med y biol **1** 80 (May) 1942

Obrador Alcalde and Pi-Suñer report on various factors which affect the cerebral edema produced in dogs by lesions of the floor of the fourth ventricle 1 Posture influences the intensity of the edema When the animal lay on one side, the edema was more pronounced in the inferior hemisphere Changing the position of the animal once the edema had appeared sometimes altered the size of the swollen hemisphere 2 Asphyxia has no effect The edema was the same whether or not artificial respiration was given This was noted to be true in spite of the fact that changes in respiratory rhythm were frequent after the experimental lesions 3 Sympathectomy has no effect on the intensity of the edema Ligation of both carotid arteries before the lesions of the fourth ventricle were produced did not prevent appearance of edema Cutting of the ligatures and reestablishment of the cerebral circulation did not increase the amount of cerebral herniation In only 1 animal, with extreme edema, did a drop in blood pressure and ligature of the carotid arteries cause mild diminution of the edema There was no change in the edema after lowering of the blood pressure in any of the other animals 4 Drugs have varying effects Intravenous injections of epinephrine caused an increase in the edema in some cases This increase was transitory and paralleled the increase in blood pressure Intravenous injection of small doses of ergotamine tartrate (0 25 mg) did not affect the blood pressure or the cerebral edema Repeated injections of small doses (up to a total of 1 mg) had no effect on the neurogenic cerebral edema The injection of larger doses (0 5 mg or more) increased the blood pressure and caused a marked increase in existent edema The injection of adrenal cortex extract (natural and synthetic), even in large doses, did not modify the edema In 6 of 9 animals intravenous injection of hypertonic solutions caused striking diminution to disappearance of the edema The edema was induced again by a new lesion in the region of the fourth ventricle and was readily diminished by a second injection of a hypertonic solution

Savitsky, New York

Experimental Epilepsy in Man Isaac Roimiser, Rev neurol de Buenos Aires **7** 241 (July-Sept) 1942

Roimiser reviews the literature on experimental epilepsy and points out that up to the present time convulsive agents have been able to produce only the motor phase of epilepsy He repeated the use of metrazol in 10 cases of various types of epilepsy, the drug being given in subconvulsive doses In all cases the seizures characteristic of the particular patient were reproduced faithfully They included petit mal, psychomotor equivalents, obnubilation, tonic spasms, clonic local or generalized convulsions and sensations similar to spontaneous auras

The drug was injected in various quantities at different times in order to obtain the optimal dose for the desired effect, 2 to 2 5 cc usually being sufficient In 1 case, in which 3 cc provoked a major spell, one-half that quantity led to an attack of petit mal The patient had suffered from both major and minor seizures

The author concludes that metrazol permits the experimental study of epilepsy in man in an objective and controllable manner In epileptic persons with adequate technic it is possible to reproduce faithfully all types of spontaneous spells, not only the typical motor crises but partial seizures, formes frustes and equivalents

PIETRI, New York

Neuropathology

SPINAL VEGETATIVE CENTERS II SPINAL TROPHIC CENTERS O GAGEL and L CZEMBIREK, Ztschr f d ges Neurol u Psychiat **171** 644 (April) 1941

Gagel and Czembirek report the case of a man aged 38 who was operated on for a perforated ulcer of the stomach Local anesthesia was used on the abdominal wall (300 cc of 0 75 per cent tetracaine hydrochloride and 1 cc of 1 per cent epinephrine hydrochloride) Gastric resection and gastrojejunostomy were performed The presence of a peptic ulcer was confirmed microscopically The drain was removed in four days, with no change in the skin Eight days later there was a discharge from the site of the drain, and in another eight days an area of necrosis of the skin the size of a 5 mark piece was noted The necrotic area spread There was a purulent discharge from the edges of this cutaneous defect The necrosis involved only skin, subcutaneous tissues and fascia, the muscle was not affected Neurologic examination revealed nothing abnormal The patient died about two months after operation, of pneumonia

That the unusual condition described by the authors was not due to the local anesthesia is evidenced by the eight day interval between the operation and the first indication of necrosis The clinical picture was not that of a spreading infection of the abdominal wall Histologic study of the cord revealed changes which may explain the necrosis of the abdominal wall Localized gliosis was found in the sixth, seventh, eighth and ninth thoracic segments, this change involved especially the so-called intermediary zone of the anterior horn cell region The cells in this region showed evidence of chronic degeneration The authors conclude that these anatomic observations point to the probability that this intermediate zone is a trophic center There is insufficient evidence to indicate that the changes in the cord were responsible for the appearance of the peptic ulcer

SAVITSKY, New York

Psychiatry and Psychopathology

AN UNUSUAL COMPLICATION OF CONVULSIVE THERAPY H H HAINES, Psychiatric Quart **18** 273 (April) 1944

Haines reports a case of bilateral fracture of the acetabulum in a 17 year old patient with schizophrenia following the second electric shock treatment The boy had also had three spontaneous convulsions in the three years prior to therapy A roentgenogram of the pelvis after shock showed deep acetabular notches on each side, with no displacement of the cracked thin fragments The lesions healed with rest and left limitation of motion in adduction and flexion The patient could walk and sit fairly well

The type of pelvis seen in this patient was first described by Otto in 1824, it has been thought by some authors to be congenital and by others to be the result of chronic disease The etiologic factors in this case remain uncertain

McCARTER, Boston

THE PSYCHOLOGY OF OBSTINACY CHRISTINE OLDEN, Psychoanalyt Quart **12** 240, 1943

Olden points out that stubbornness originally meant heroism and that psychologically obstinacy is a way of fighting to establish supremacy In childhood it

is a means of combating the threats imposed by the environment, later it is used to combat the threats of the superego

Obstinacy is a protection against feelings of guilt and fear and is a means of combating anxiety, especially anxiety rooted in feelings of inferiority and humiliation It enhances the feeling of omnipotence whenever self esteem is threatened by some real object or by the superego, since self esteem is unstable in obstinate people Obstinacy is a function of the ego which develops during the anal period, for obstinacy is holding back for the purpose of opposing, but it also has an oral root in the baby s screaming when he wants to enforce his will

Passive obstinacy is a compromise between aggressive feelings and anxiety It is a good method of bolstering the self esteem but fails because it produces secondary guilt feelings and because it often conflicts with reality

The analyst s attitude is important in analyzing obstinate patients He should not meet obstinacy with counterobstinacy He can help the patient by strengthening his ego through freeing him of his fears of the analyst He can help by confronting the obstinate attitude with reality He can increase the patient's self esteem by praising his efforts

PEARSON, Philadelphia

THE CONCEPTION OF THE REPETITION COMPULSION EDWARD BIBRING, Psychoanalyt Quart **12** 486, 1943

The concept of the repetition compulsion is a complex one and has at least two aspects 1 The repetition compulsion is the expression of the inertia of living matter, of the conservative trend toward maintaining and repeating intensive experiences 2 It is a regulating mechanism, with the task of discharging, in fractional amounts, tensions caused by traumatic experiences after they have been bound

The two meanings are not identical The first meaning may be called a restitutive tendency and the second a repetitive, or reproductive, tendency Freud used the term "repetition compulsion" to cover both meanings, sometimes referring to one and sometimes to the other He attributed acting out in analysis and in life to the repetitive tendency, whereas he used the concept of the restitutive tendency as evidence supporting the assumption of two types of primal instincts However, he used only the restitutive tendency of the repetition compulsion to characterize the life instincts, and not at all the repetitive tendency This definition leads to a contradiction as to what are life instincts and what are death instincts Freud regarded the repetition compulsion as a regulating mechanism which helps the psychic apparatus either to discharge incoming stimuli completely or to reduce them to the lowest possible level This concept, however, divides the repetition compulsion into the automatic process of binding because of the need for protection against intensive stimulation and the consequent mechanical trend toward abreaction of the accumulated tensions This does not seem satisfactory and raises the following questions What is the nature of the conservative principle, with its repetitive and restitutive tendencies? What is the relation of these tendencies to each other? Is the restitutive tendency only a special instance of the mechanical trend toward discharge of bound energies, or is it an active tendency?

The repetition compulsion may be defined as the tendency toward automatic or impulsive repetition, and eventually discharge, of painful (traumatic) experiences This definition gives certain criteria the automatic or impulsive nature of the repetition, the painful character of what is repeated (These two criteria correspond solely to the repetitive tendency) There is a kind of spontaneity, i e, the repetition will occur for internal reasons only, there will be a decrease of the intensity of the tensions (These two criteria correspond to the restitutive tendency)

Hartmann has given the most complete enumeration of the various kinds of repetitions According to him, repetition occurs "(1) in response to the same stimuli, (2) when what was experienced resulted in pleasure or was pleasurable in itself, (3) in connection with automatisms of thought and action (4) when interested actions were not completed, (5) when traumatic experiences

have not been assimilated The last-mentioned example corresponds to the repetition compulsion

From clinical examples the author shows that the restitutive tendency is a function of the ego while the repetitive tendency is a function of the id The restitutive tendency is not a defense mechanism of the ego, however, but is part of the working off of mechanisms of the ego the function of which is to dissolve the tension gradually by changing the internal conditions which give rise to it They are not abreactions, although abreaction in small doses may take place during the process

The ego tends to try to manage the repetition compulsion If the repression which brings the repetition compulsion into play ceases to exist, the ego is called on to deal with the relaxation of the repetition compulsion and the new formation of the instinct through detachment of the libido or through compensation and adaptation through familiarity If the repression remains, the ego may be weaker than the repetition compulsion and may be completely dominated by it Or the ego may be stronger and may deal with the repetition compulsion actively by absorbing it, as in the case of destiny neuroses The real problem is the relation of the repetition compulsion to the pleasure principle

Freud assumed that instincts clung to primary or intense experiences and followed the way paved by these experiences irrespective of pleasure or pain He considered this a fundamental characteristic of instinctual drives The repetition compulsion is an instinctual automatism There is no fundamental difference between fixation and repetition compulsion except that a fixation is the link between an instinctual drive and pleasurable experiences, while the repetition compulsion is the result of a link between instinctual drives and any intense experiences, whether pleasurable or not

The repetition compulsion is beyond the pleasure principle but is not absolutely opposed to it It exists prior to the pleasure principle, and it is broader, since it can fix both the pleasurable and the painful Once the repetition of the painful has been accepted as beyond the pleasure principle, it can easily be seen that the ego secondarily may use this repetition to obtain pleasure

PEARSON, Philadelphia

SELF PRESERVATION AND THE DEATH INSTINCT ERNST SIMMEL, Psychoanalyt Quart **13** 160, 1944

Simmel attempts to advance another theory concerning the dualistic theory of instincts, which differs to a certain extent from Freud's views Freud's theory of instincts was always based on one principle, that of dualism reflecting the dynamics of two instinctual and opposing energies His first concept was that of a conflict between self preservation and sexuality His final concept was that of an instinctual conflict within the ego, a struggle of one part of the ego, which desires to keep alive, against another part, which desires to destroy itself

Simmel's theory substantiates Freud's view that the fundamental conflict which binds and disrupts extraindividual life is also responsible for all intraindividual disturbances, i e, an internal conflict between constructive and destructive principles, a conflict between love and hate He considers the destructive energies to be manifestations not of a death instinct but of the instinct of self preservation This makes the need for self preservation a libidinal component of the ego and constitutes an apparent contradiction in ascribing destructive tendencies to it, for libido is supposed to bind substances, not to aim at their disruption and destruction

There is no contradiction however, if the development of Freud's theories of libido and instinct are reviewed, particularly the modifications of the original theory which were necessary when the concept of narcissism was introduced This made the previous qualitative prerequisite for sexual libido, the provision of organ pleasure, lose its significance It was replaced by the view of a quantitative distribution of narcissistic libido within the ego The original concept of the pleasure-pain principle—i e, to provide pleasure and to avoid pain—was enlarged into the

concept of a principle which tended to keep libidinal tension within the ego below the level where pain was experienced When this did not occur, i e, when there was a quantitative disturbance in the equilibrium of narcissistic libido, anxiety developed Self preservation is an attempt to preserve the coherence of the structual unity of the ego by means of an adequate distribution of narcissistic libido, i e, it is the ego's tendency to keep itself free from anxiety

Self destruction is a cardinal principle in nature, but it shows only one of the characteristics of an instinct, the aim of removing excitation Self preservation has all the characteristics of an instinct Its origin lies in the instinct to devour Its organic source is the gastrointestinal tract Its aim is to remove stimuli from the gastrointestinal tract, and its object is food Its ultimate aim in the deep unconscious is that of self preservation and self development, in contrast to the ultimate aim of the sex instinct, i e, reproduction

Freud defined libido as energy aiming at the synthesis of living substances, and even the apparent destructive energy of the instinct of self preservation fits this definition and so places it in the category of libidinal energies It seeks to achieve this aim simply within the individual, while the sex instinct seeks to achieve the aim outside the individual The gratificaton of the sex instinct removes the excitation and retains the object The gratification of the instinct of self preservation removes the excitation and destroys the object The instinct of self preservations aims at the reinstatement of the equilibrium of narcissistic libido It aims primarily at reinstating as much as possible complete instinct repose This condition is only maturing from the primitive object relation, governed by hate, to the civilized object relation, governed by love

Nirvana is the basic attraction of all progressive trends which constitute mental disorders Rank was correct in his view of the significance of the trauma of birth for the genesis of the neuroses, but he failed in his interpretation One does not want to repeat the trauma of birth, but one has to repeat the aggressive alimentary act by which one was able to annul that trauma

In the psychoses the ego abandons genital primacy and gives in to the gastrointestinal primacy In the transference neuroses the ego is arrested on the way to its ultimate aim of regression by stages of libidinal object fixation where there already exists a fusion of immature sexual libido with gastrointestinal libido Neuroses and psychoses reflect a defense by the ego against the dangerous consequences of regressively awakened destructive devouring tendencies Basically, the ego is caught between two attractions, that of preserving the frustrating object and that of preserving the narcissistic equilibrium In the transference neuroses it decides in favor of the object, in the psychoses, in favor of instinct repose

Simmel's theory may be summarized as follows

There is a devouring instinct in man which is closely associated with the need for self preservation The process of identification which ends the Oedipus conflict substitutes for and wards off incorporation, which is the result of the ego's regression to the primacy of the gastrointestinal instinct Failures in this process precipitate a morbid psychopathologic state, which turns self preservation into self destruction by subjecting the ego to the attracting power of the Nirvana principle

PEARSON, Philadelphia

PSYCHOSURGERY AN EVALUATION OF TWO HUNDRED CASES OVER SEVEN YEARS
WALTER FREEMAN and JAMES WATTS, J Ment Sc **90** 532 (April) 1944

Freeman and Watts first describe the technic of their operation Different patients require the severing of different amounts of white matter Patients with schizophrenia and obsessional neuroses of long standing require more extensive cuts than patients with pure affective psychoses About 20 per cent of their patients have required a second operation, and some have required a third The performance of a second operation may cause considerable inertia and incontinence It may be done any time after the first If the patient does not show the inertia and dis-

orientation anticipated, or if the incisions are shown by roentgenographic examination to be poorly placed (iodized oil is placed in the incision to make the tract visible), the incisions may be repeated in a few days

The authors find that the two chief features in the two weeks following lobotomy are indolence and lack of tact The patients are apt to show euphoria or exuberance but with petulance on being thwarted There is distractability and no desire for perfection But in the course of months or years improvement sets in Some patients continue to improve five years after operation Some are said to be even more productive than ever in their lives

Of 154 living patients operated on at least six months previously, 61 per cent were usefully occupied, and only 12 per cent had to be confined to institutions The patients with severe emotional tension have done best and the alcoholic patients worst

Autopsy of 8 postlobotomy brains has shown cystlike cavities beneath small cortical incisions The cortex at the frontal pole shows no demonstrable change "There are some degenerated fibers (Marchi) anterior to the lesions, particularly in the upper quadrant The most striking alteration is the severe degeneration of the nucleus medialis dorsalis of the thalamus Here the cells in the lateral portion of the nucleus have undergone a reduction of 75 per cent or more with some shrinkage of the nucleus as a whole and a little reactive gliosis The pathologic findings indicate the thalamofrontal radiation has been fairly completely severed

Whether this is the only pathway of importance in the operation of prefrontal lobotomy has not been determined, since rather restricted incisions aimed at the fasciculus cinguli have also produced striking alterations in the patient's behavior, but more particularly along the lines of autonomic alterations"

In summary, the authors believe "that prefrontal lobotomy abolishes many of the symptoms of mental disorder by bleaching the affect attached to the ego Symptoms such as anxiety, worry, apprehension, obsessive thinking and the like are prominent in most of the psychoses at least during their inception These symptoms have the egocentric signature The threat to the security and integrity of the individual is magnified by himself By reducing the emotion expended upon the ideas relating to the self, prefrontal lobotomy reduces the significance of the self to the self and tends to abolish egocentricity"

McCARTER, Boston

NEUROSIS AND INTELLIGENCE H J EYSENCK, Lancet **2** 362 (Sept 18) 1943

Eysenck studied the relation of neuroses to intelligence as measured by the results of the progressive matrix test on about 3,000 neurotic men and women Of these subjects, a little less than 500 were women, for whom it is said that the test has not been as well standardized as for men Over 3,000 male army recruits were used as controls The outstanding finding was the absence of a difference in the average intelligence levels of the neurotic subjects and the controls The nearest thing to a difference between the normal and the neurotic subjects was the fact that a larger number of neurotic subjects showed an intelligence level which could be classified as a little above or a little below the average for the test, whereas a greater number of normal subjects were rated as of average intelligence

The author believes that his observations support the view expressed by others that the so-called lower intelligence of neurotic persons is caused by a weakness in the efficiency of mental functioning rather than by their inability to abstract and reason

McCARTER, Boston

MYXOEDEMA AND PSYCHOSIS H ZONDEK and G WOLFSON, Lancet **2** 438 (Sept 30) 1944

Zondek and Wolfson report the case of a previously healthy woman of 23 in whom all the signs of myxedema developed after delivery of a normal, healthy child The most striking feature was the development of true schizophrenia, for which she was admitted to a mental disease hospital eighteen months after delivery and treated, with little improvement, with insulin and electric shock

At the end of the eighteen months she was given Thyroidin, 0 2 Gm four times a day, and by the fourth day her urinary excretion had risen from 1,000 to 2,700 cc The psychosis was better in this short time and cleared in a fortnight There was no change in the basal metabolic rate at the time the mental change was first evident, of the objective signs, only the urinary output altered Her voice was clearer, the reflexes were more active and the palpebral fissures wider by the end of the first fortnight A year later she was still physically and mentally well and was still receiving 0 2 Gm of Thyroidin daily in alternate weeks

The authors believe that the favorable effect of the drug was due to dehydration of the cerebral tissue

McCARTER, Boston

PSYCHOTIC EPISODES IN PSYCHOPATHIC PERSONALITIES EDUARDO BRUCHER ENCINA, Rev de psiquiat y disc conexas **9** 128, 1944

The author reports on the occurrence of psychotic episodes in patients with psychopathic personalities in a hospital in Chile during the period from 1941-1943, inclusive There were 61 patients with psychopathic personality among 4,631 admissions during the three years (1 3 per cent), 44 were men and 17 women Forty-nine (80 3 per cent) were discharged, 25 recovered, the condition of 16 was improved, and 8 showed no improvement Paranoid types, perverts, amoral psychopaths, unstable personalities and patients with hyperthymic syndromes predominated The author notes excitement, depression and schizoid and delirium-like reactions among the types of psychotic episodes seen in this group He believes that the concept of psychopathic personality has a sound basis and is clinically valuable

SAVITSKY, New York

Meninges and Blood Vessels

MENINGITIS IN CHILDREN CHARLES H HOLLIS and JAMES MARVIN BATY, New England J Med **230** 278 (March 9) 1944

Hollis and Baty report their observations in 28 consecutive cases of meningitis in children There were 9 children with influenzal meningitis, 12 with meningococcic meningitis, 5 with pneumococcic meningitis, 1 with meningitis due to the colon bacillus and 1 with meningitis due to infection with Salmonella All but 3 of the patients were less than 3½ years of age

The authors conclude that combined treatment with specific antiserum and a sulfonamide compound is advisable in cases of influenzal and pneumococcic meningitis In treatment of meningococcic meningitis sulfonamide therapy is adequate except in cases of fulminating meningococcic infection

The therapeutic results were as follows Two patients of the 9 with influenzal meningitis and 2 of the 12 with meningococcic infection died, both of these were infants with acute meningococcemia and presented the Waterhouse-Friderichsen syndrome Four patients out of the 5 with pneumococcic meningitis died All were under 8 months of age The infant with colon bacillus meningitis survived, after

a course of treatment with sulfathiazole, but blindness and atrophy of the optic nerve resulted The infant with meningitis due to Salmonella oranienburg did not respond to sulfathiazole and died

GUTTMAN, Philadelphia

CAUSALGIA AND GANGRENE RARE COMPLICATIONS IN MENINGOCOCCAL MENINGITIS PHINEAS BERNSTEIN, New England J Med **230** 482 (April 20) 1944

Bernstein reports the case of a 34 year old woman with meningococcic meningitis, for which she was successfully treated with sulfadiazine, who later had gangrene of several toes and areas of the skin and causalgia of the right upper extremity The causalgia disappeared about three and a half months after the onset of the illness

GUTTMAN, Philadelphia

Diseases of the Brain

SUBACUTE DEGENERATION OF THE BRAIN IN PERNICIOUS ANEMIA RAYMOND D ADAMS and CHARLES S KUBIK, New England J Med **231** 1 (July 6) 1944

Adams and Kubik report their observations on 2 patients with pernicious anemia who not only had evidence of involvement of the posterolateral column but exhibited psychiatric symptoms One patient had "acted queerly for several weeks" prior to admission and subsequently lapsed into a stupor and died The other patient had a history of being "vague as to details of her illness and was irritable and difficult to manage"

The pathologic changes in the brain and spinal cord in both patients were almost identical The important anatomic changes consisted of a diffuse, uneven degeneration of nerve fibers in the spinal cord and the cerebral white matter, with relatively little proliferation of fibrous glia The lesions in the brain resembled those in the spinal cord so closely that there could be little doubt concerning their identity

The authors favor the supposition that both subacute combined degeneration of the spinal cord and subacute degeneration of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary for the metabolism of myelinated nerve fibers Also, they state that it is not to be expected that every patient with pernicious anemia will have demonstrable cerebral lesions, but all those in whom there are definite and widely disseminated cerebral lesions will probably have mental disorders

GUTTMAN, Philadelphia

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF POLYCYTHEMIA VERA W S TINNEY, B E HALL and H Z GRIFFIN, Proc Staff Meet Mayo Clinic **18** 300 (Aug 25) 1943

Tinney, Hall and Griffin report a number of cases of polycythemia vera in which difficulties referable to the central nervous system were manifest

They first mention symptoms and signs reported by other observers in cases of this disease Impaired memory, lethargy, depression and delusions, tinnitus, apprehension, psychoses, insomnia, excitability, epilepsy, aphasia and cerebral thrombosis or hemorrhage have all been mentioned Headache, scotomas, paresthesias and vertigo have also been found Focal localizing signs have sometimes been so prominent that operation for cerebral tumor has been performed Symptoms referable to the nervous system have seemed to point to a functional disorder Sometimes mental deterioration or paralyses have been present

The authors found symptoms referable to the nervous system in 127 of their 163 cases of polycythemia vera Headache was the most frequent symptom and

was not characteristic in location though most often generalized The following tabulation summarizes the manifestations of the disease referable to the central nervous system, with their distribution in the present series

Symptoms	No of Cases
Headache	59
Vertigo	52
Weakness and fatigue	41
Nervousness	29
Visual disturbances	28
Severe neuroses with exhaustion	27
Paresthesias	23
Aphasia	13
Loss of consciousness	10
Tinnitus	8
Mental depression	7
Complications	
Cerebral thrombosis	27
Suspected cerebral tumor	8
Choked disk	4
Herpes	1
Combined sclerosis	1

The authors point out that objective neurologic signs were found in 17 per cent of their cases Objective signs were of progressive nature in 8 cases, so that cerebral tumor was suspected They state that when there is uncertainty as to which entity is causing the cerebral signs—polycythemia or tumor—treatment for the former should be tried first The reduction in blood volume should result in lessening of signs of involvement of the nervous system unless there is permanent injury following thrombosis or hemorrhage Progression of symptoms should lead to suspicion of a mass-expanding lesion

McCARTER, Philadelphia

OBSERVATIONS ON THE TOE FLEXOR (SCHRIJVER-BERNHARD) AND TOE-FANNING REFLEXES H H FLEISCHHACKER, J Ment Sc **89** 403 (July-Oct) 1943

Fleischhacker discusses the Schrijver-Bernhard reflex and the toe-fanning phenomenon The former is elicited by tapping with a percussion hammer over the tibia or the adjacent muscles A plantar flexion of the small toes is considered a positive reaction The toe-fanning phenomenon is elicited by applying "the now usual technique for testing Oppenheim's reflex, which is somewhat different from that originally used by Oppenheim Care should be taken to exert pressure only on the skin not on the tibial muscles '

The author found these reflexes to be five or six times as frequent in patients with catatonic schizophrenia as in patients with other mental disorders of functional type They occur at least as often as "the usual psychomotor symptoms (catalepsy, pulling, resisting—taken together) It may be claimed therefore that the phenomena are of a differential diagnostic value The S B reflex is characteristic for a certain type of subcortical extrapyramidal disorganization, while the fanning phenomenon is apparently released by cortical disturbances"

In a group of normal controls, under conditions of muscular contraction assumed in order to simulate catatonia, there were a number of positive responses, but a true Babinski sign was not elicited

The author also found that the two reflexes described predominated on the left side in a majority of the catatonic patients

McCARTER Boston

Diseases of the Spinal Cord

POLIOMYELITIS ON THE ISTHMUS OF PANAMA CARL E TAYLOR, New England J Med **230** 790 (June 29) 1944

Taylor reports observations in 72 cases of anterior poliomyelitis in the Gorgas Hospital, Canal Zone, over a thirty-eight year period, from 1904 to 1942 The average incidence was 1 case of poliomyelitis in about 7,000 admissions to the hospital Eight hospital cases were not included in the study group because they failed to meet the rigid diagnostic standards or because the infection had not been contracted on the isthmus

Taylor noted that the crest of the seasonal curve occurs during November, December and January—the end of the rainy season Most of the patients resided in urban areas Poliomyelitis was about three times as common in white persons as in Negroes Of the white persons, 52 per cent were 5 years of age or under, as compared with 85 per cent of the West Indian Negroes and 83 per cent of the Panamanians There were twice as many males as females among the white patients and the Panamanians, but the incidence in the two sexes was equal among the West Indian Negroes

GUTTMAN, Philadelphia

Peripheral and Cranial Nerves

THE RAMSAY HUNT SYNDROME NORMAN R SHUMACK and MILTON H KIBBE, J Nerv & Ment Dis **101** 9 (Jan) 1945

The syndrome of herpes zoster auricularis with facial palsy and auditory symptoms was first described by Ramsay Hunt in 1907 and has been infrequently reported since The authors describe the case of a 27 year old soldier who was hospitalized because of vertigo, inability to close the right eye and pain in the right ear Examination revealed right-sided facial palsy of peripheral type, redness of the right concha, nerve deafness in the right ear, hypalgesia and hypesthesia of the right side of the face and absence of the right corneal reflex The next day a herpetic eruption appeared on the concave surface of the right concha Spinal tap on the eleventh day revealed that the fluid was under normal pressure, with a count of 44 cells per cubic millimeter, of which 95 per cent were lymphocytes Improvement was progressive, and by the thirty-fourth day the patient had completely recovered

The authors believe that this case lends support to the view that herpes zoster is a trophic expression of fairly localized inflammation of the central nervous system

CHODOFF, Langley Field, Va

LOCALIZED NEURITIS OF THE SHOULDER GIRDLE J D SPILLANE, Lancet **2** 532 (Oct 30) 1943

According to Spillane, cases with unusual neuritic features have come to be recognized in the armed forces which were not observed before the war in such numbers The author himself has seen 20 such cases, and he has studied the records of others A fairly clear clinical picture has emerged of what may be called localized neuritis of the shoulder girdle In 42 of these 46 cases the onset of the illness was characterized by sharp pain about the shoulder The painful sites were usually along the upper border of the trapezius muscle and over the spinatus muscles and the belly of the deltoid muscle Pain was sometimes felt along the inner border of the scapula, in the axilla or up the side of the neck Many patients said it was severe and burning, and nearly all of them needed analgesics The pain was commonly worse at night and disturbed or prevented sleep It was aggravated by the patient's lying on the affected side and persisted acutely for from three to fourteen days, thereafter it rapidly subsided, but in a few cases a chronic ache was complained of for six or seven weeks The pressure of braces or the weight of a gun

or pack aggravated the discomfort Pain was more severe in the muscles which subsequently showed atrophy The muscles affected were the serratus magnus, spinatus, deltoid, trapezius, sternocleidomastoid and rhomboid Effective movements of the shoulder girdle were greatly hampered The wasted deltoid muscle, with paralysis of abduction, the hollowed supraspinous and infraspinous fossae of the scapula and the winging of the scapula, alone or in various combinations, produced a striking deformity of the shoulder girdle The usual forms of treatment for neuritis did not seem to alter the course of the illness If a patient with this condition is seen for the first time some months after the acute phase, the malady may be mistaken for poliomyelitis The author differentiates the condition from poliomyelitis, acute brachial radiculitis and neuritis He considers the possible role of "injection neuritis" and of repeated minor traumas The preponderance of cases of right-sided neuritis and the selective nature of the muscle wasting suggest that "injection neuritis" is not an important factor It is quite possible that the long thoracic and suprascapular nerves could be injured by carrying a weight (pack and rifle) across the shoulder Many of the patients, however, were employed in sedentary posts, and in 26 of them the illness developed during convalescence in hospital

J A M A

Treatment, Neurosurgery

TREATMENT OF NARCOLEPSY WITH DESOXYEPHEDRINE HYDROCHLORIDE L M EATON, Proc Staff Meet, Mayo Clin **18** 262 (July 28) 1943

Eaton found that of 15 patients with the chief complaint of narcolepsy, 12 showed subjective improvement with the use of desoxyephedrine hydrochloride, and he expressed preference for this drug to amphetamine, tried previously Desoxyephedrine hydrochloride was given in 2 5 mg tablets in the morning, at noon and at 4 p m With 3 patients the last dose was omitted because it produced insomnia None of the patients was bothered by other untoward effects of the drug Two patients preferred amphetamine Evaluation of the response was based entirely on letters from the patients Patients showed improvement over periods of six to seventeen months

MCCARTER, Boston

USE OF THE RESPIRATOR IN TREATMENT OF BARBITURATE INTOXICATION MANUEL FALCON G, Arch de neurol y psiquiat de Mexico **6** 299 (Sept-Oct) 1943

The author suggests artificial respiration in an "iron lung" for patients with severe barbiturate intoxication which fails to respond to strychnine, coramine or picrotoxin Bulbar symptoms are often the cause of death Respiration is often seriously defective The author reports only 1 case, that of a woman aged 26, who was desperately ill when placed in the respirator She was pulseless and unconscious, the blood pressure was not obtainable, and she had corneal areflexia and evidence of anoxemia In thirty hours after being placed in the respirator she was able to breathe by herself, after forty-eight hours she regained consciousness, and after five days she was transferred home Unfortunately, pneumonia developed, and she died forty-eight hours after leaving the hospital In spite of the tragic outcome in this case, the author recommends use of the respirator in cases of severe and desperate barbiturate intoxication

SAVITSKY, New York

Congenital Anomalies

UNUSUAL CONGENITAL ANOMALIES OF THE LUMBO-SACRAL SPINE (SPINA BIFIDA) J M MEREDITH, J Nerv & Ment Dis **99** 115 (Feb) 1944

Meredith reports 3 unusual cases of spina bifida The first was that of a 6 year old girl previously treated for an infection of the urinary tract who proved to have a complete spina bifida (occulta) throughout the entire lumbar portion of the spine

and the sacrum At operation large portions of the posterior bony canal below the twelfth thoracic and the first lumbar vertebra were observed to be absent, and the terminal roots of the cauda equina were gathered together in a cable of nerves, which extended along the sacrum posteriorly to a dimple in the skin just above the gluteal cleft This was released, affording relief of tension on the cauda equina The operation resulted in considerable improvement in the patient's sphincter control This case illustrates the results of abnormal fixation of the cord or cauda equina in precluding the rostral migration which normally occurs with the lengthening of the spine

The second case was that of a 22 year old man with weakness and atrophy of the left leg, saddle and genital anesthesia and marked bladder disability, in which roentgenograms revealed a pronounced congenital deformity of the sacrum At operation the conus medullaris was found to be adherent to the inner dura at the level of the second bony segment of the sacrum on the left, it was surrounded by a large pad of fat Partial freeing of the conus relieved tension on the cord and resulted in considerable postoperative improvement

The third case was that of a 13 year old girl who had had a simple lumbosacral meningocele repaired at the age of 3 years, with excellent results and entire absence of symptoms until three months before the present admission, when severe pain in the legs and slight dysuria developed There was a complete spinal fluid block, and myelographic examination with iodized poppyseed oil revealed a mass lesion at the level of the third lumbar vertebra, which after operative removal proved to be a large cholesteatoma Postoperative recovery was complete The author believes this combination of a large congenital tumor and a simple meningocele to be unique

CHODOFF, Langley Field, Va

News and Comment

COURSE IN RORSCHACH TEST, MICHAEL REESE HOSPITAL

The Division of Neuropsychiatry, Michael Reese Hospital, announces its 1946 course in the Rorschach test, to be conducted June 3 to 7, inclusive, by S J Beck, Ph D The teaching this year will focus especially on the more severe neurotic conditions The Rorschach records to be demonstrated will therefore be those derived from patients in acute conflict, including veterans of the war For information, write to the secretary, Division of Neuropsychiatry, Michael Reese Hospital, Twenty-Ninth Street and Ellis Avenue, Chicago 16

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

HAROLD G WOLFF, M D,

Chairman, Section of Neurology and Psychiatry, in the Chair

Combined Meeting, Feb 13, 1945

Electroencephalographic Changes Associated with Psychopathic Personalities DR OSKAR DIETHELM and DR DONALD J SIMONS

The well person is self dependent, he recognizes the need to adapt to life around him and is able to do so Abnormalities of behavior designated by the term "psychopathic" may affect a person's self dependence or his relationship to his environment, and very often both In the past, these behavior disorders have been considered from the point of view of their relation to the well known forms of psychoses Other groupings have been formed on the basis of the type of difficulties which were most obvious In this presentation we shall classify psychopathic personalities according to the disturbance of function of the personality From a psychopathologic point of view, one may find disturbances of the organization of the personality or an exaggeration or underdevelopment of various groupings of personality features Psychopathic personalities, in which the organization of the personality is primarily disturbed, may be due to late maturing, i e, psychologic immaturity as compared with the chronologic age Another disorder, frequently related to immaturity, is characterized by looseness of organization of the whole personality, thus permitting contradictory strivings and acts Its opposite is expressed in loss of plasticity, as seen in the rigid personality Examples of psychopathic maladjustment based on exaggeration of various personality features are found in the excessively moody, the poorly adjusted socially or the poorly adjusted ethically It is also important to evaluate the genetic and dynamic factors In some psychopathic personalities constitutional factors predominate In others, psychoneurotic and other psychodynamic factors prevail

From a study of all patients with psychopathic personalities admitted to the Payne Whitney Psychiatric Clinic in the last two years the following patterns emerged 1 Definite psychoneurotic type The psychoneurotic reactions may have had their recognizable onset in childhood, in adolescence or in early adult life but they resulted in such a degree of social maladjustment that the diagnosis of psychopathic personality seemed indicated

2 Cyclothymic type Patients with this type showed maladjustment because of pronounced and easily provoked mood swings These patients often utilized psychoneurotic factors

3 Persons with poor ethical standards and resulting social difficulties The patients showed irresponsibility, with disregard for consequences, lack of persistence of emotional relationships and absence of emotional depth The symptoms were stealing, untruthfulness, truancy and irresponsibility toward debts

4 Loose organization of the personality and immaturity The patients were characterized by unsatisfactory emotional control, contradictory strivings, poor self discipline and frequently a rebellious attitude toward authority and society The patients were of the aggressive, as well as the passive, type

5 A generally inadequate personality with vague thinking Some of the patients had high ethical standards, others, unusually low They were of the aggressive as well as of the passive type

The 61 patients in this study were tested in the course of routine electroencephalographic examinations Interpretations were made without knowledge of the clinical picture or the diagnosis Records were made on a two channel ink-writing oscillograph of the Grass type Some of the patients were given 100 Gm of dextrose by mouth before the test was made in order to eliminate the possible occurrence of slow waves due to low blood sugar In a few cases the blood sugar level was determined, and the results led us to believe that all the patients had a blood sugar level above 100 mg per hundred cubic centimeters at the time of the test

Forty-nine per cent of the patients in this series had abnormal records The psychoneurotic and cyclothymic groups showed normal records The abnormal electroencephalograms, which were confined to the other three groups, may be divided into four types records showing low voltage fast activity, records showing 5 to 7 a second activity, records showing low voltage slow activity and miscellaneous abnormal or doubtful records In the group of patients with poor ethical standards, moderately slow, 5 to 7 a second, activity was the predominating abnormality (58 per cent) The group characterized by immaturity and poor emotional control had poorly defined electroencephalographic records The records for the group of inadequate personalities were made up primarily of low voltage slow activity (64 per cent of the record)

Since no type of abnormality is absolutely characteristic of one type of psychopathic personality, it is not possible to make a diagnosis from the record Further, we do not claim that all records showing low voltage fast, low voltage slow or 5 to 7 a second activity are those of psychopathic personalities This point has not been studied

Since neurologic examination of all our patients revealed no defects, and since the patterns differ to a striking degree from those seen in cases of structural disease of the brain, we believe that there is no evidence of structural changes Therefore we infer that some types of psychopathic personality have a defect in the physiologic functioning of the brain

DISCUSSION

DR BERNARD L PACELLA The paper by Drs Diethelm and Simons presents some fascinating and important observations An impressive aspect of the presentation concerns the method of subdividing the psychopathic groups into categories which appear to be scientifically valid for purposes of laboratory investigation In contrast to what has been presented here, the literature contains much electroencephalographic investigation of psychiatric disorders in which the clinical groupings are not clearly defined for purposes of careful laboratory study For this reason, controversy prevails regarding the incidence of abnormal tracings in different psychiatric disorders

It is of interest that the patients with psychopathic personalities of the psychoneurotic and cyclothymic types all exhibited normal electroencephalograms, whereas those with poor ethical standards, exhibiting a lack of persistence in emotional relationships, lack of emotional depth and aggressive or antisocial behavior, all had abnormal electroencephalograms This striking difference in electroencephalographic patterns between two such types of psychopathic personalities is almost startling Of course it is open to question whether all persons who could be classified in either category would maintain the 100 per cent normal or abnormal record, and I am quite certain that the authors themselves would not necessarily anticipate such a finding if they had much larger groups for study However, even if these figures were extended in some degree by the addition of more subjects in the group under investigation, I doubt whether the significance or implications of the observations presented this evening would be altered

It should be kept in mind that the electroencephalogram is essentially a silhouette, or a summation, of cerebral electrical activity, which, in turn, is intimately related to the physiologic activity and the functioning of the brain

It is likely, therefore, that a disturbance in the physiologic or functional organization of the brain which might be manifested in an abnormal electroencephalogram may also be manifested in abnormal behavior of the organism Just as there are grades of anatomic anomalies and congenital histologic disturbances in the brain which may be associated with deviate behavior, so there may be grades of functional anomalies and constitutional physiologic disturbances also associated with certain types of abnormal behavior which may be revealed by a finer technic, such as the recording of the electroencephalogram

The question may arise whether environmental factors which impose continued stress or provide for faulty development of the personality functions may produce a disturbance in cerebral physiologic activity which could be reflected in the electroencephalogram Although my colleagues and I have a few cases in which this seems a likely possibility, our observations indicate that it is far more probable that in the great majority of instances a faulty constitutional cerebral organization has been the originally important factor as a determinant, or at least a concomitant, of the disturbance in behavior

This statistical presentation of the electroencephalographic abnormalities is in essential conformity with the observations of other investigators and tends to support some of our own studies on delinquent children It might be of interest here to note that patients who have a history of psychopathy in members of the family are more likely to show abnormal records than are other persons

Certain questions arise which are not mentioned in the paper, although I am sure they must have been considered by the authors First Were patients excluded from this study if they had previously been subjected to severe head trauma or had had encephalitis or were blood relatives of epileptic persons? Were any of the patients receiving barbiturates or other medicaments which might conceivably have produced an effect on the electroencephalogram? I should be interested in knowing also whether the abnormal features were of diffuse nature over the entire cortex or whether they were more prominent in some particular region of the brain Both phylogenetically and ontogenetically the frontal cortex appears to be the last to develop and to become organized physiologically in the brain, and I wonder whether the abnormal activity might not generally be more prominent or more frequent over the anterior aspects of the cerebral hemispheres This, I may say, has been our experience in patients of the psychopathic types under discussion

Dr Donald J Simons No patient having convulsions was included in this group No patient with a recent head injury was included I do not believe that any of the patients were receiving barbiturates at the time of the test Abnormalities were most prominent in the frontal and parietal regions In some patients they were present in the occipital areas, in others they were seen in the parietal and frontal areas only

Dr Gustav Bychowski What changes were observed in the records of homosexual persons? I understand from Dr Diethelm's personal communication that a number of the patients who were studied were homosexual

Dr Donald J Simons I cannot answer that question Perhaps Dr Diethelm has such information

Dr Oskar Diethelm I omitted a discussion of homosexual patients Some of them fell in the group of psychopathic personalities, in others the disorder was of psychoneurotic origin The electroencephalographic patterns vary considerably and have not been studied sufficiently

Dr Harold G Wolff I should like to ask Dr Pacella whether the disturbances described by Drs Diethelm and Simons were in any way related to those he described in the records of his anxious patients at the last meeting

Dr Bernard L Pacella Apparently they are not The patients who showed a great deal of anxiety often exhibited a prominent alpha rhythm The waves sometimes were almost continuous, without the interruption of low voltage fast

activity, which is ordinarily noted between alpha "spindles" I might add that other subjects, who may have the usual amount of tension when coming into the electroencephalographic room, may reveal patterns which are in some instances similar to the tracings described by the authors for their psychopathic patients and which would ordinarily be considered normal However, I believe that in the authors' records the waves had a significantly higher amplitude, which would then classify them as abnormal

Natural History of "Sciatic Neuritis" DR HENRY SHANKLAND DUNNING (by invitation)

In recent years a common neurologic disease called sciatic neuritis has been found to be caused, in the majority of cases, by herniation of the nucleus pulposus of a lower lumbar intervertebral disk with pressure on nerve roots of the cauda equina I maintain that the symptoms and signs of herniation of the nucleus pulposus in the fourth lumbar or the lumbosacral intervertebral disk are indistinguishable from the well defined syndrome that was formerly called sciatic neuritis Cessation of pain after removal of a herniated nucleus has been so impressive that whenever this characteristic syndrome appears the question of spinal operation demands consideration However, cessation of pain has been observed without spinal operation with sufficient frequency to justify the supposition that the defect may be repaired by natural processes In order to verify this supposition the present study was undertaken, which consisted in finding out what has happened to patients who had so-called sciatic neuritis before the operation for removal of the disk was presented

Follow-up data were obtained on 55 patients with a condition which was reliably diagnosed as sciatic neuritis and which, after careful consideration of the symptoms and signs, would beyond reasonable doubt now be classified as probable herniation of the nucleus pulposus of the fourth lumbar or the lumbosacral intervertebral disk Most of these patients were private and ward patients in the New York Hospital All had pain in the posterior or posterolateral aspect of one leg which was increased by stretching the sciatic nerve of the affected leg Additional symptoms and signs were pain in the lumbosacral region, tenderness in the region of pain, increase of pain by raising the intra-abdominal pressure, as in straining during defecation, diminished intensity or absence of the ankle jerk and weakness of muscles, paresthesia and decreased cutaneous sensation in the distribution of the fourth lumbar through the second sacral nerve root The methods of treatment were numerous, but none of the patients had a spinal operation The follow-up period began with the first attack of pain which was reliably diagnosed as sciatic neuritis and ranged from one year and three months to twenty-three years, with an average of five years and one month

The patients were divided into the following groups on the basis of the follow-up data

1 Patients who have been continuously free from pain in the leg and the lower part of the back since the subsidence of the first attack The duration of pain in the leg ranged from eleven days to three years, with an average of seven months The period of recovery ranged from one to seven years and eight months, with an average of three years and five months

2 Patients who have had persistence, recurrence or development of pain in the lower part of the back since the subsidence of pain in the leg Inconsequential and considerable degrees of pain were reported, but none of the patients mentioned disability from it

3 Patients who have had persistence or recurrence of pain in the leg with or without pain in the lower part of the back Three degrees of pain could be defined inconsequential, and not interfering with former activity, considerable, but permitting relatively light work, disabling, or not permitting any material physical work In the last category were placed the 5 patients who eventually

had a spinal operation, with resulting relief from pain in each case In 3 cases the operation was referred to as "spinal fusion", in 1, as "spinal operation," and in the last the operation is known to have been the removal of a herniated nucleus pulposus in the fourth lumbar intervertebral disk The results of follow-up observation are shown in table 1

The follow-up data offered an opportunity to determine whether the prognosis for so-called sciatic neuritis could be predicted from the abnormalities found on neurologic examination or lumbar puncture The neurologic signs consisted of diminished strength or absence of the ankle jerk, muscular weakness and decreased cutaneous sensation The only abnormality observed on lumbar puncture was an elevation of the total protein content of the spinal fluid The incidence of these abnormalities in the patients for whom the prognosis was satisfactory was compared with the incidence in the patients for whom the prognosis was unsatisfactory In the group with a satisfactory prognosis 50 per cent of the patients had an impaired ankle jerk, in the group with an unsatisfactory prognosis the incidence was 48 per cent The incidence of muscular weakness and decreased cutaneous sensation was somewhat higher for the patients whose prognosis was satisfactory In the group with a satisfactory prognosis the total protein of the spinal fluid

TABLE 1.—*Results for 55 Patients with "Sciatic Neuritis" Who Were Followed One and One-Fourth to Twenty-Three Years*

	Satisfactory		Unsatisfactory	
	Number	Per Cent	Number	Per Cent
Free from pain	20	36		
Pain only in lower part of back				
Inconsequential	2	4		
Considerable			2	4
Pain in leg				
Inconsequential	8	14		
Considerable			16	29
Disabling			7	13
Total	30	54	25	46

exceeded 45 mg per hundred cubic centimeters for 8 of the 14 patients who had a lumbar puncture, in the group with an unsatisfactory prognosis it was elevated in 5 of the 12 patients who had a lumbar puncture Thus, it appears that prognostic predictions cannot be based on the neurologic signs or on the protein content of the spinal fluid

For the purpose of therapeutic evaluation, Dr Bronson Ray has submitted his data in 100 cases at the New York Hospital in which he operated for removal of a supposed herniated nucleus pulposus in the fourth lumbar or the lumbosacral intervertebral disk In earlier times the symptoms and signs in these cases undoubtedly would have led to the diagnosis of sciatic neuritis The operative procedure and the lesions found at operation, with their incidence, were as follows removal of a herniated nucleus pulposus, 76 cases, removal of an unherniated degenerated nucleus pulposus from a ruptured disk, 13 cases, decompression of nerve roots without removal of the nucleus pulposus from an incompletely ruptured disk 3 cases, no diseased disk, 8 cases In table 2, the results in 82 of these cases in which follow-up observations were made for six months or longer are compared with the results noted in follow-up observation in the cases in which no operation was performed

Conclusions.—Of the syndrome formerly called sciatic neuritis, and now known in the majority of cases to be caused by herniation of the nucleus pulposus of the fourth lumbar or the lumbosacral intervertebral disk, the prognosis is satisfactory without spinal operation in 54 per cent of cases

Although removal of the herniated nucleus promptly relieves pain and betters the prognosis by 32 per cent, natural processes should be given an opportunity to repair the defect before spinal operation is urged

Neurologic signs and spinal fluid protein are of no prognostic value

TABLE 2.—*Follow-Up Observations in Eighty-Two Cases of Herniated Nucleus Pulposus Treated Surgically*

	No Operation (55 Cases) per Cent	Operation (82 Cases) (Ray) per Cent
Recovery		
Residual symptoms	36	60
Inconsequential	18	26
Considerable	33	12
Disabling	13	2

DISCUSSION

DR BYRON STOOKEY Dr Dunning has brought to our attention an interesting and intriguing problem, one that has been presented to all who were seeing cases of so-called sciatic neuritis ten years ago, before herniation of the nucleus pulposus was recognized I am sorry to disagree with a good deal of what he has said I am not at all in agreement that in the cases in which the condition was called sciatic neuritis the trouble was in fact herniation, for there are a large group of cases in which the symptoms, by all the tests I know, are identical with what I should call herniation, yet operation has failed to show herniation What is the cause of the pain in these cases? The oxygen epidurograms, which my associates and I at the Neurological Institute find to be very satisfactory, better by far than the gas myelograms, show no herniation, but in a few cases the symptoms have been so definite and the signs so distinct that we felt we were justified in operating Yet no herniation was found We have another group of cases of what in former days would have been called sciatic neuritis and is today called herniation in which we have had a defect in the air column, yet at operation no herniation was found In these two groups of cases the condition could certainly be called sciatic neuritis since we have pretty well demonstrated that it is not due to herniation These cases, I think, belong to the group in which the patient gets well without operation What the trouble is I do not know I do know that there is a group of cases at the Neurological Institute of what we call gluteal myositis in which the patients get well with roentgen therapy There are other groups of cases in which there are similar disturbances of the mechanism of the lower part of the back and the patients get well without operation I think that if Dr Dunning were to continue the interesting study he has made, and were to include cases in which he had established the diagnosis of herniation, either with air or with an opaque substance, and then were to make follow-up studies in these cases, as he has suggested, he would have a group comparable to that in which operation is employed In other words, the question, I gather, is this Why rush into operation, since formerly many of the patients got well and the outlook for them was satisfactory? I doubt very much that this attitude is valid The only way to settle the question is to carry out conservative treatment in alternate cases of herniation in which the diagnosis is proved, so far as it can be proved, and to compare them with the cases in which operation has been employed Personally, having seen the herniations at operation, it is inconceivable to me that the patients could recover with any conservative treatment, unless it be with some form of manipulation I have a distinguished friend in the Washington University School of Medicine who has had sciatic pain, and he has a colleague who puts him through a maneuver that gives him relief, so that whereas he could not move before, within five minutes he can move However, he got tired of going for treatments and

decided to have an operation No herniation was found He still has the pain and is most uncomfortable, but he is relieved by manipulation

I should like to ask Dr Dunning what form of treatment he would suggest for trial before one resorts to operation My own impression is that if the diagnosis is established as well as one can establish it operation is indicated I agree that cases of this type are not happy ones for the surgeon to encounter I have had many failures—many cases in which I do not find herniation I wish I were one of those neurosurgeons who have a 100 per cent record of successful removal I am sure, however, that from the old group of disorders called sciatic neuritis one distinct condition, that is herniation, has been picked out There remain other conditions in that group which need to be reclassified

DR BRONSON SANDS RAY Dr Dunning has compared his observations with the operative results in the first 100 cases of diseased disk in which operation was performed at New York Hospital as he implied, but perhaps did not stress, in many of the 100 cases of so-called ruptured disk operation did not actually show herniation Nevertheless, in some of the cases in which there was no apparent herniation degeneration of the disk was present, even old tears in the annulus fibrosus without any nucleus pulposus remaining In other cases, as Dr Stookey has implied, the surgeon is unhappy in finding nothing at all that can be diagnosed as disk disease My notion has been and I suspect that I have influenced Dr Dunning somewhat in his attitude that often when no frank protrusion of the disk is found at operation there is reason to believe that there has been disease of that disk which has served to change the local anatomic structure, if you like, and thereby to put the nerve root or roots in that region in such a position as to be easily injured by some motion or stress of the back I have still considered such a condition to be a disease of the disk, and I believe that it would be entirely unfair to call it protrusion, or herniation, of the nucleus pulposus Certainly, the problem is still a much debated one, and I agree entirely with Dr Stookey that the surgeon does not have an easy time He finds himself called on more frequently to account for the failures than he does to help celebrate the successes

I believe that some of the patients Dr Dunning included in his study had such a short illness that they would not have been considered subjects for operation It may be that these patients with early spontaneous recovery would have a better prognosis than those who go on for some time before operation is performed

DR HENRY SHANKLAND DUNNING Dr Stookey asked me how I should treat patients who have this syndrome I know of no better treatment than rest in bed and I suppose that, since patients firmly maintain the value of the device, they should rest on a bed board

With respect to Dr Ray's last comment, 1 patient who recovered had pain in the leg for only eleven days, the others were ill for longer periods, up to three years, the average duration being seven months

DR BRONSON SANDS RAY Did any of the cases occur in the last eight years, since operative treatment has been in use?

DR HENRY SHANKLAND DUNNING Yes, indeed, many of them

DR HAROLD G WOLFF I think Dr Dunning stated that seven months was the average time required for recovery

DR HENRY SHANKLAND DUNNING Seven months was the average duration of pain in the leg in the group of patients who made a complete recovery after the first attack

DR HAROLD G WOLFF How does that compare with the period for the operative procedure, from the beginning of pain until the patient was back on the job?

DR HENRY SHANKLAND DUNNING When a patient has a protruding nucleus removed, the period is cut down to just the time of recovery from operation

DR HAROLD G WOLFF What are the facts, Dr Ray?

DR BRONSON SANDS RAY I do not know that I can give figures, but I am sure the period of recovery would be under seven months

DR HAROLD G WOLFF Three months?

DR BRONSON SANDS RAY I should think so

DR A M RABINER I am confused as to the purpose of this paper Does Dr Dunning mean to tell us that there is no such thing as sciatic neuritis, that all pain in the lower part of the back, of radiating character, is due to a slipped disk, or is he saying that all patients with sciatic pain which persists have herniated disk?

DR HENRY SHANKLAND DUNNING When a patient presents himself with the syndrome that used to be called sciatic neuritis, I have no way of telling whether it is sciatic neuritis or disk disease At present patients are frequently urged to have an operation early in the course of the disease, whatever it is I did not wish to give the impression that I think that in all these cases the pain is caused by disk disease

DR A M RABINER You mean that you do not know whether there is such a thing as sciatic neuritis?

DR HENRY SHANKLAND DUNNING That is so

DR PETER G DENKER At Bellevue Hospital my colleagues and I face this problem frequently, and we have found it helpful to call in the orthopedists who, with their roentgenographic technic, provide objective evidence of disease of the disk Dr John McCauley, of the orthopedic department, has shown us cases in which by tilting the patient to one side and then the other the roentgenograms of the lumbar region of the spine showed absence of compression of the intervertebral space where the herniated disk was present We have not found Dr Stookey's procedure of injection of air of much help but have learned to place more diagnostic importance on elevation of the protein of the spinal fluid

On the whole, we feel more optimistic about the surgical approach in these cases than would be indicated by the authors It is my impression, after my experience with such cases in the past five or six years, that the neurosurgeons have a good deal to offer and that the results obtained have been far better than they were in past years, when the condition was always called sciatic neuritis and treated with rest and supportive measures

I cannot help but comment on the title of this paper, which, in my opinion, could just as well have been called "Natural History of Disease of the Intervertebral Disk" One must think of the latter entity as an illness with remissions, just as one thinks of multiple sclerosis or pernicious anemia in similar fashion It is not at all unusual to see the patient recover from his first attack spontaneously, sometimes one even obtains a history of two or three attacks in the past I therefore rarely advise operation during the first attack unless it is unusually severe or persistent One cannot but be impressed with the fact that in these days a diagnosis of sciatic neuritis is made rarely, since it has come to be realized that in most cases the disease is really a traumatic lesion of the intervertebral disk with radicular symptoms of sciatic pain

DR BYRON STOOKEY I should like to ask Dr Denker whether, when he speaks of injections of air as being of little value, he has tried the epidurographic method, that is, the introduction of air outside the dura We first used subarachnoid injections and found it very difficult to get an adequate picture of the area between the fifth lumbar and the first sacral vertebra, we got fairly good pictures between the fourth and the fifth lumbar vertebrae and excellent pictures above that, so we finally gave up that procedure and relied on the epidurogram I wonder what Dr Denker's experience has been with the epidurogram

DR PETER DENKER We have not used the epidurogram, our injections have been subarachnoid

DR LEO M DAVIDOFF It seems to me that the cases Dr Dunning has described are clinically so classically like the cases of herniated disk that certainly all of them certainly could not have been instances of conditions other than herniated disk in other words, some of the patients must surely have had a herniated disk and have recovered Therefore I cannot entirely agree with Dr Stookey that the patients who improved had "sciatic neuritis" because of some other factor and for that reason got well without operation We see patients who prove to have diseased disks who do get well, as in the cases Dr Denker described I know a man who had his first attack twenty years before a recurrence, and after the recurrence a ruptured disk was found at operation His second attack was exactly similar to the one occurring twenty years before, therefore the question in my mind is not whether patients with herniated disk associated with the sciatic syndrome can improve but whether the improvement is permanent I believe most of the patients will have another attack and when they do they probably will have an operation It is perhaps unwise to operate at the time of the first attack, and it is my attitude that when the patient is having his first attack or has just had it, he should be left alone and then operated on when has a recurrence

DR HAROLD G WOLFF What is the rate of recurrence in the series at the New York Hospital?

DR BRONSON SANDS RAY I am not sure that I can give the figures and I should want to qualify my answer by distinguishing between persons who have recurrent backache and those who have recurrent sciatica I believe that the recurrence of pain in the back after an operation for injured disk is 40 per cent and that the recurrence of sciatic pain is approximately 10 per cent

Acute Alterable States in Multiple Sclerosis DR C RAY FRANKLIN (by invitation) and DR RICHARD M BRICKNER

Several years ago a patient at the Neurological Institute had sudden brief attacks of blindness I observed pronounced spasms of his retinal arterioles during these attacks Subsequently I presented the case before the Section of Ophthalmology of the Academy of Medicine The patient had disseminated disease of the central nervous system but not the typical syndrome of multiple sclerosis

Within the past year Dr Brickner and I have observed 13 patients with true multiple sclerosis who showed similar phenomena Some were from Mount Sinai Hospital and some from the Neurological Institute Some of them had sudden attacks, and others were still suffering from impaired vision of recent onset Scotomas could be plotted, spasms of retinal arterioles could be seen and both could be instantaneously relieved with injection or inhalation of vasodilator drugs

In addition, 2 patients with multiple sclerosis with associated morning diplopia obtained instantaneous relief by inhaling amyl nitrite

Another patient, with mild intention tremor, suffered a decided increase in the tremor on smoking a cigaret This effect could be prevented by an intravenous injection of papaverine hydrochloride or by the drinking of liquor

These observations led us to the hypothesis that there may be a connection between the arteriolar spasms and the symptoms and that the spasms may be the cause of the lesions in the nervous system Whether this is true or not under these conditions one is free from the problem of spontaneous remissions and other complex, long term characteristics of the disease These are acute states instantaneously alterable, and they furnish a condition in which isolated controllable experiments can be performed (Slides were shown illustrating (1) the arteriolar spasms [paintings] (2) the scotomas immediately before and immediately after administration of the drugs (3) diplopia before and after inhalation of amyl nitrite, and (4) straight lines drawn by the patient with intention tremor, showing the effects previously described)

Comment—We have not been able to study controls with diplopia and scotomas from other causes Dandy has reported a case of aneurysm of the carotid artery in which ptosis was improved with cold baths Shumacher and Wolff described transient relief of changes in the visual fields associated with migraine with small amounts of amyl nitrite

We wish to mention a case of permanent hourglass spasms in which a paradoxic reaction occurred with use of vasodilators—the constriction became narrower and extended farther along the involved arterioles

DISCUSSION

DR HAROLD G WOLFF Can the authors draw any conclusions from these observations?

DR RICHARD M BRICKNER Only those I mentioned These observations led us to the hypothesis that there may be a connection between the arteriolar spasms and the symptoms and that the spasms may be the cause of the lesions in the nervous system What impressed us was not that spasms and scotomas were present but that they were present simultaneously and could be reduced or abolished together Dr Rucker, at the Mayo Clinic, described spasms in two retinal veins, but he did not associate them with visual disturbances, we think that the spasms can be linked up with visual disturbances, a hypothesis which gives our observations their interest

DR LEON H CORNWALL Since 1913 a number of theories regarding the cause of multiple sclerosis have been advanced by numerous authors, including Gye, Marinesco, Kuhn and Steiner, Simons, Rothfeld, Freund, Hornowski, Brickner and Putnam Strong evidence against its transmissibility by inoculation methods or against an organismal origin has been presented by a group of workers, including Siemerling and Raecke, Hauptman, Burley and Dudgeon, Magnus and Teague The work of Teague seems to me to deserve more widespread notice than it has received With the modesty which so often characterizes those who devote their lives to research, Teague considered his negative results as unimportant and never published them, except in a brief note in 1922 He devoted one year full time to an investigation of the disease His work was done in the laboratories of the department of neurology, Columbia University, under a grant from the Commonwealth Fund The material for his study consisted of injections of blood and cerebrospinal fluid from 16 persons suffering with multiple sclerosis, and these injections were made into a total of 219 animals—including guinea pigs, rabbits, 2 dogs and several monkeys His conclusion was that there is no evidence to substantiate the belief that multiple sclerosis is due to a spirochete or to any other organism or that a disease with similar clinical symptoms can be transmitted to the animals that he used by the inoculation of blood or cerebrospinal fluid Assignment of the pathologic examination of the material removed by Dr Teague was made to me after Dr Teague gave up this work Briefly, there was no evidence of any lesions that resembled multiple sclerosis in any of the animals that he had inoculated

In 1927 I injected cerebrospinal fluid from a patient with rapidly progressing multiple sclerosis into the lumbar sac of a Macacus rhesus monkey and at the same time injected fluid into a rabbit and a guinea pig Observations on these animals revealed no evidence of disease after ten months In 1930 Dr Groszberg and I attempted to produce the disease in animals (rabbits) by the injection of blood from patients suffering from multiple sclerosis When we terminated the experiments we had injected material from 23 patients into over 70 rabbits As controls, the blood from presumably normal persons was injected into 20 rabbits I shall not review that work now The results were rather interesting but not particularly significant It is true that the animals given injections of blood from patients suffering with multiple sclerosis manifested a greater incidence of symptoms indicating neurologic disease, but we did not feel that this had enough importance to warrant a report

The same vascular phenomena responsible for the ocular changes in the 13 patients observed by Dr Franklin and Dr Brickner might, I think, play a role in the causation of multiple sclerosis At least, such a speculation seems to me permissible This appeals to me as much more reasonable than some of the other pathologic, physiologic and chemical observations which have been postulated as having a possible causal relation to multiple sclerosis I do not know just what Dr Brickner's attitude is now to the role of esterases in multiple sclerosis, nor do I know just how strongly Dr Putnam feels that venous thrombosis in itself is causative, but it has been my personal feeling that the observations reported by these two workers are merely incidental, and not in any sense related to the fundamental cause or causes of this interesting disease I do not know whether every patient with multiple sclerosis has an increased esterase content of the blood, and a somewhat similar remark might be made regarding the presence of venous thrombi I do feel, however, that the observations that Dr Brickner and Dr Franklin have reported this evening may contribute to the discovery of the etiologic factor or factors more than anything that has preceded, and I shall be interested to hear Dr Wolff's comments

DR S BERNARD WORTIS I wonder whether Dr Brickner has any cases of multiple sclerosis that he has studied in which these phenomena have not been found, also, has he observed these changes in the retinal vessels in patients with vascular disease without associated neurologic signs and symptoms?

DR HAROLD G WOLFF I take it these patients have no other vascular disease —hypertensive or other arterial disease

DR RICHARD M BRICKNER No, there was no evidence of other vascular disease

Of the patients who did not show the spasms, some had no visual symptoms others may have had visual symptoms and we missed the arteriolar changes I defer to Dr Franklin in the observations on the retina I have thought that I saw beautiful spasms and have sent the patient to Dr Franklin, only to be told that there was no spasm Dr Franklin has limited himself to changes in the vessels that are extremely definite, and any doubtful ones have not been included Another point Sometimes these phenomena are transient They may be there for just a few minutes I had a patient at Mount Sinai Hospital with visual symptoms that seemed to come and go, she was treated with histamine, and her vision was better after each infusion I looked at the fundi, in company with Dr Drooz, the resident in neurology, we each saw, independently, one vessel in the patient's retina which was opening and closing almost like a fist as we looked at it—Dr Franklin has seen a number like that I saw it first and asked Dr Drooz to look, without telling him what I had seen, he saw the same thing It was never observed again, and no other vascular abnormality has been seen in this patient's fundi

DR PETER G DENKER I should like to ask Dr Brickner whether all these patients had diffuse lesions of multiple sclerosis or whether they represented cases of retrobulbar neuritis that was presumptively multiple sclerosis

DR RICHARD M BRICKNER No, they were all cases of true multiple sclerosis except for Dr Franklin's first case at the Neurological Institute In this case there was diffuse disseminated disease of the nervous system, but not the kind of process which for these purposes we should call multiple sclerosis, although it probably is There was a case at Mount Sinai, that of a youth of 17, who was there for the study of fever with hives, one day he suddenly declared that he was blind, several members of the house staff found a great blanching of one retina, I don't think there was time for any of the attending physicians to see it He had a number of these attacks while in the hospital, and he has had about fifteen since That was over eight months ago There was nothing neurologic about the case, and we are interested in following the patient to see whether he ever does have multiple sclerosis

Reactions Following Electric Shock Treatment DR JOHN FROSCH, DR DAVID J IMPASTATO, DR LILLY OTTENHEIMER (by invitation) and DR S BERNARD WORTIS

Electric shock treatment frequently produces clinical by-products of interest Most frequent is the organic confusion which arises in the course of treatment and persists for some time afterward We should like to call attention to another interesting clinical syndrome which we have encountered and which has been referred to in other reports The treatments were given daily, and each patient received a preconvulsive intravenous injection of sodium amytal Treatment was continued until the patient became confused and his clinical symptoms subsided

Essentially, the picture consisted in an acute psychotic episode starting a few days after treatment was discontinued and lasting several days to several weeks The reactions observed represented something more than the usual organic confusion which arises in the course of treatment and persists for some period afterward, It appeared that after treatment was discontinued the patient showed the usual memory defects and confusion, which differed little from the picture seen in our other patients In a few of the patients in whom psychotic episodes developed the subjective reaction to the memory difficulties and confusion was more pronounced A few days to a week after treatment was discontinued an acute psychotic picture developed, which lasted from a few days to a few weeks These psychotic episodes took different forms, but all had in common the feature that the patient was disturbed, agitated, restless, assaultive and destructive, and occasionally stuporous In some instances the patient was demanding, suspicious and paranoid In the main, however, the gross clinical picture of the psychotic episode was different from the psychiatric picture seen before shock treatment was instituted

That the development of the psychotic reaction did not have any direct correlation with the degree of confusion was also manifested by the fact that sometimes as much as a week elapsed after treatment was terminated before the psychosis developed During this interval the confusion frequently lessened It might well be that as the confusion subsided sufficiently the patient's awareness of his defects became more pronounced in those cases in which psychosis developed It was as though the tolerance of the ego to the defects and to the distortions of the body image was not so good in these patients as in those who did not have the complication

It appeared to us that the organic changes caused by electric shock were not entirely responsible for the development of the psychotic episodes The fundamental personality structure in its reaction to the organic damage appeared to be important

All the developing psychotic reactions subsided, and the most that happened was that the patient was left with his previous psychiatric picture With the clearing of the engrafted psychotic picture most of our patients also showed improvement in their original clinical complaints Once having discontinued shock therapy, one must wait, therefore, before reinstituting it when such a reaction develops

DISCUSSION

DR ROBERT B MCGRAW The title of this paper also is somewhat misleading As a matter of fact, on reading the paper carefully one finds it is a discussion of a particular psychotic complication seen after a certain number of treatments of a certain character of depressed patients in the second decade of life All these patients were subjected to in excess of ten grand mal seizures over a relatively short period, and most were given daily treatments I mention the intensity of the treatment because work is being carried out with different modalities in an effort to produce seizures and to avoid, at the same time, the electroencephalographic abnormalities, or at least to keep them minimal Even though I am not one to be much disturbed by the permanent damage to the cortex from electric shock and

am inclined to feel that memory disturbance is not entirely without benefit, I feel one should not allow the reactions to proceed too far, particularly in patients of the affective reaction type Possibly my interest in ambulatory shock therapy has made for more conservatism, and I may have erred on the side of giving too little treatment, but I have had some patients who have recovered and maintained recovery with as few as three or four treatments, a fairly large number with five and many with six All the patients reported on here received more than that I believe that even for depressive reactions these patients were treated a bit too long and too frequently The authors themselves suggest this, at least with respect to the daily treatments Schizophrenic reactions may need more prolonged treatment and manic excitements may do well with daily treatments for a short period With the summary of the paper I am almost entirely in accord The authors mentioned Dr Kalinowsky's paper, given at Philadelphia In that paper he emphasized organic factors in psychotic manifestations complicating electric shock treatment In the present paper underlying personality factors and psychogenic factors are emphasized There is no doubt in my mind that different people react differently to the same amount of memory change, even though this change may be fairly slight The awareness of this change may come about some time after the treatments have been discontinued

DR OSKAR DIETHELM While listening to this paper, I was reminded that at the First International Psychiatric Congress, held in 1924, after World War I, malaria treatment was presented, and great attention was paid to the fact that in a number of the cases of dementia paralytica in which cure was effected a paranoid picture developed I remember that Bleuler arose and said that these reactions were manifestations of latent schizophrenia When there was no longer much malaria treatment of severe dementia paralytica, these psychotic reactions became rather infrequent I was also reminded that in 1936, when Dr Joseph Wortis came back from Vienna, he told us about severe reactions to insulin treatment He mentioned regression of the personality to the infantile stage I mention this because such observations do not relate merely to electric shock treatment but seem to occur with two similar forms of treatment when far-reaching therapy is used

DR LOTHAR B KALINOWSKY Dr Diethelm is correct in stating that similar reactions are also found with insulin treatment, though less frequently They likewise occur with metrazol treatment I think one must understand them, in the light of other symptomatic psychoses or organic reaction types, as occurring with infectious-toxic diseases or any other interference with cerebral function In a paper presented before the American Psychiatric Association (Organic Psychotic Syndromes Occurring During Electric Convulsive Therapy, ARCH NEUROL & PSYCHIAT **53** 269 [April] 1945), I tried to show that one sees in electric convulsive therapy the whole series of organic reaction types, from slight confusional states to severe Korsakoff syndromes, hallucinoses, delirium-like pictures and, finally, deep dementia-like states When the patient comes out of a quiet confusion, he sometimes passes through a more productive state, as described by the authors Organic reactions can be largely avoided by limiting treatments to two a week, but in hospitals these reactions should not be feared, for, as the authors pointed out, they always clear up in a week It is of great interest to study the choice of symptoms A psychoneurotic patient with a schizoid personality will more readily present a schizophrenia-like organic syndrome, with delusions and hallucinations, whereas a cyclothymic personality is predisposed to an organic reaction with manic-like or depressive features Thus one can foretell from the patient's original personality what type of symptoms he will show These observations during electric convulsive therapy confirm the view that the clinical picture of an organic reaction, i e, the choice of symptoms, is not determined by the type of the noxious agent, in electric convulsive therapy the agent is always the same, and yet various patients present a great variety of organic syndromes In accordance with obser-

vations on patients with other symptomatic psychoses, it seems that the same patient in several courses of electric convulsive treatment may react each time with the same clinical picture

DR S BERNARD WORTIS May I emphasize two points? First, I would speak a word of caution to persons using electric shock treatment, second, I wish to point out that this syndrome occurred in a patient who was given the treatment three times a week The confusion alone is not productive of this particular psychotic reaction

DR HAROLD G WOLFF Do I understand that all these patients recovered?

DR S BERNARD WORTIS Yes

DR DAVID J IMPASTATO It should be made clear that psychotic reactions following electric shock therapy are uncommon, and few patients have them I have given treatments once a week, twice a week, three times a week and every day Most of our patients have been treated twice a week We now have over 400 patients who have been treated twice a week Of these 400, only 1 had a psychotic reaction like that described this evening In general, one may say that these psychotic reactions occur infrequently in patients treated once or twice a week and that most of them occur with the daily treatment If you want to obviate them, do not treat patients daily

Why are patients with depressions given daily treatments? Such patients were given daily treatments at Bellevue Hospital because we thought we might be able to shorten the period of hospitalization We have found that daily treatment did not achieve this and have discontinued this regimen for depressions We have obtained excellent results in treating depressed patients twice a week, and they should be so treated except perhaps at the beginning if the patients are suicidal or severely depressed, when treatment three or four times a week for the first week is indicated

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BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

MADELAINE R BROWN, M D, *Presiding*

Regular Meeting, Feb 15, 1945

Histopathologic Effects of Anoxia on the Central Nervous System DR L RAYMOND MORRISON and DR STANLEY COBB

This paper was published in full in the January 1946 issue of the ARCHIVES page 1

DISCUSSION

DR C G TEDESCHI, New York There is little that one can add to the discussion of a paper presented by Dr Morrison and Dr Cobb Many years ago Dr Cobb, at that time working in association with Dr Gildea, showed that ten to fifteen minutes of practically complete cerebral anemia will induce permanent lesions Later, other investigators, including Heymans and associates and Weinberger and Gibbon, showed that the lethal period is shorter by several minutes and Sugai and Gerard, through electroencephalographic studies, demonstrated that the time required for the disappearance of potentials in the brains of animals with cerebral anoxia varied from ten seconds to two minutes in different parts of the brain of the same animal Yet the classic description by Gildea and Cobb of the intimate neuronal changes accompanying the phenomenon of anoxia remains unchallenged This evening Dr Morrison and Dr Cobb have taught us something more about cerebral anoxia—that it results in a process of intensive demyelination of scattered distribution They have stressed the difficulty that they encountered in detecting the presence of fat in the affected areas of demyelination I found

myself in the same difficulty not long ago while studying the brains of animals subjected to head trauma under various experimental conditions Among the observed changes, moniliform swelling of the myelin sheaths and their breaking down, absorption and resolution into round, oval or irregularly shaped globules were frequently found In these demyelinated areas, the sudan III and Marchi methods almost constantly failed to reveal the presence of fat droplets, and only in a few instances could droplets be seen in the oil red O preparations, with pyridine solvent At that time Dr Benda gave me an explanation of the phenomenon, and I am sure we will all appreciate hearing from him on this point

Evidence of vascular injury, especially of the blood capillaries, has long been recognized as one of the most constant pathologic manifestations of death from asphyxia, and the members of this society remember the beautiful demonstration by Campbell, Alexander and Putnam of such injury in the brain substance May I ask Dr Morrison whether, in his opinion, the patchy distribution of the lesions he has shown is due to a vascular factor or to a difference in sensitiveness to the anoxic agent of the various areas of the brain?

There is another point I should like to bring up in the discussion The occurrence of hyperglycemia during asphyxia and other conditions, such as emotional disturbances, has been known since the early investigations of Claude Bernard and has recently been emphasized by Britton, Hill and others The increase in blood sugar in these conditions is thought to be due to an outpouring of epinephrine, which causes augmentation of the rate of hepatic glycogenolysis and discharge of sugar into the blood May the cellular changes that the authors have just described and compared with the changes seen in fatigue be related to these metabolic disorders?

Dr Clemens E Benda, Wrentham, Mass It is hardly necessary to congratulate the authors on this paper, for every neuropathologist must have liked to listen to it I wish to make one comment only on the changes in the myelin There is no doubt from the slides presented that there is true degeneration of the myelin and that the paleness of the white matter is not artificial I feel that it is not accidental that Dr Morrison failed in his attempts to stain the broken-down myelin with fat stains From my own material, as well as from the literature, I am under the impression that degenerated myelin gives a positive reaction to fat stains only if the myelin is catalyzed by action of other cells, whether nerve cells, glia cells or phagocytes If free myelin is broken down without the action of cells, the broken-down material is not catalyzed to a state of neutral fats accessible to the so-called fat stains The balls of degenerated myelin stain with various methods, but they are not broken down to the level of free fat I should like to ask Dr Morrison whether he has had the same experience

Dr L Raymond Morrison In answer to Dr Tedeschi's question about the focal and general, widespread regions of demyelination, and as to whether I think there is a relationship between the focal types and the blood vessels, I do not know I have frequently seen in my preparations that when the patch of demyelination was small it often had in its center a blood vessel, while in the extensive, widespread areas of demyelination there was no special relation to blood vessels

I could have shown a few slides illustrating the increased cortical activity of the adrenal glands, which, as was shown by Thorn and his co-workers, is the basis of the mechanism for transforming proteins into carbohydrate The association of hyperglycemia with anoxia is well known, and that was of great interest to me in the early days of this experiment, for I thought that if there were increased sugar in the blood and increased glycogen in the liver, since the brain metabolizes only glucose and since the amount of oxygen was cut down so that the brain could not oxidize all the glucose, there might be excess sugar in the brain Therefore for a long time I looked for glycogen in the brain It is hard to find glycogen One has to work very fast I could not use liquid air, the animals were too large to be decapitated I froze the brain tissue in situ, fixed it in absolute alcohol in situ, and so on After a while I learned that there is no excess glycogen there

under the conditions of anoxia, for the metabolic processes are reversed and anaerobic, instead of aerobic, glycolysis takes place, so that even more sugar is consumed than under normal conditions

I am interested in Dr Benda's information about the relation of fat in the tissues to the cell reaction It seems good, and there must be something in it As I think of some of my slides, the situation was precisely as Dr Benda has stated

Histologic Changes in the Brain Resulting from Various Anoxic Conditions MAJOR F H LEWEY, Medical Corps, Army of the United States

It is still an open question whether the effect of nitrous oxide and carbon monoxide on the brain is solely that of anoxia, or, in other words, is identical with that of high altitude Histologic changes in the brain similar to those following anoxia were to be expected if this was the case No studies directed along this line could be found in the literature

The same problem exists with respect to the correlation between the degree of oxygen tension or concentration in the blood in various noxious conditions and the resulting damage to the brain A correlation between the fortuitous circumstances of human pathology and specifically designed animal experiments must be effected to open an approach to these problems

The brains which formed the basis of this study were those of 3 patients who died after exposure to nitrous oxide, carbon monoxide and strangulation, respectively All 3 patients showed the same typical picture of decortication Such patients cannot be kept alive longer than eleven days, even under the best nursing care The material is, therefore, comparable clinically and with respect to the survival time No data could be obtained concerning the concentration of carbon monoxide in the blood of 1 of the patients Certain conclusions about it may be drawn from comparison with material gained in well controlled animal experiments

The brains of the persons who had died of nitrous oxide and carbon monoxide poisoning showed extensive necroses, more pronounced in the cortex in the first and in the white matter in the second In the former the glial reaction was prominent, in the latter there was no glial or mesodermal reaction These changes were more intensive than those found in the average case of carbon monoxide poisoning in men, and comparable alterations are equally rare in experimental animals because animals so strongly intoxicated do not survive long enough to show histologic changes

My experiments indicate that in dogs a histologic picture comparable to that described in man requires a concentration of carboxyhemoglobin in the blood of 90 per cent To this end, dogs were intoxicated in a closed rebreather system with pure carbon dioxide mixed with oxygen until cardiac standstill occurred The dogs were resuscitated by transfusion with oxygenated red blood corpuscles, in addition to artificial respiration

Correlation of the histologic changes in the brain with the concentration of carbon monoxide in the blood of dogs suggested that 75 per cent carboxyhemoglobin represents a critical level below which even intoxication prolonged over many hours fails to produce pronounced changes, in contrast to the intense alterations of the brain tissue from short-lasting intoxications above that level

Electrocardiographic and electroencephalographic tracings during prolonged carbon monoxide poisoning in dogs strongly suggest that the primary cerebral disturbance occurring with carbon monoxide poisoning is reversible and that the characteristic changes in the brain are secondary to the circulatory collapse

The brain of the patient who tried to hang himself failed to show any histologic changes with the same magnification and staining methods as those applied in the cases of nitrous oxide and carbon monoxide poisoning Finer methods of examination with higher magnification are needed to show the damage which is actually present This mechanism is best visualized by staining the hemoglobin in the cortical blood vessels Such slides indicate that certain cortical areas are void of circulation The opinion that this phenomenon is caused by anoxia, and not by

interruption of circulation in the carotid arteries during strangulation, is strengthened by its duplication in another brain after death from pure anoxia corresponding to an altitude of 36,000 feet (11,000 meters) A further corroboration of the qualitative difference of the histologic changes in the brain following carbon monoxide poisoning, on the one hand, and pure oxygen deficit, on the other, was found in an experiment on two series of dogs, in one of which the animals were exposed to small doses of carbon monoxide and showed the typical changes in the brain, although of low grade The other series, which was kept in the underpressure chamber for the same length of time in an atmosphere containing an even slightly lower partial oxygen pressure than that produced by the carbon monoxide, failed to show any histologic changes

To sum up The histologic changes in the brain following nitrous oxide and carbon monoxide intoxication in man are similar Those following a corresponding degree of pure anoxia are different This observation does not support the opinion that nitrous oxide and carbon monoxide act exclusively through the resulting anoxia The varying histologic pictures following inhalation of carbon monoxide depend mainly on the degree of concentration of carboxyhemoglobin in the blood above 75 per cent The direct effect of carbon monoxide, and possibly of nitrous oxide, on the brain seems to be reversible, whereas the well known pathologic changes appear secondary to the circulatory collapse following myocardial anoxia, which does not occur until a carboxyhemoglobin concentration of 75 per cent is reached

DISCUSSION

Dr Bronson Crothers I should like to ask Major Lewey about the age of the patients We have seen repeatedly, after accidents of birth or carbon monoxide poisoning, for example, children who have become completely decerebrated and idiotic Apparently, in children under 4 years of age the percentage of fatalities is not nearly as great as among adults

Dr C G Tedeschi, New York Major Lewey has already made other contributions to the field of cerebral anoxia and has shown that exposure over a long period to small amounts of carbon monoxide, generally considered within the safety limits, is far from harmless In my opinion, the observations he has presented this evening are still more important, as they show that the histologic changes in the brain following exposure to nitrous oxide and carbon monoxide are different from those following a corresponding degree of pure anoxia The most logical conclusion, as he stressed, is that nitrous oxide and carbon monoxide do not act exclusively through the resulting anoxia Might I ask Major Lewey whether the observations on the brain were extended to the myocardium and, if so, whether a different pathologic process was displayed in the latter under the different anoxic conditions?

Dr Jacob E Finesinger I should like to ask Dr Lewey about that experiment in which carbon dioxide got in by mistake What percentage of carbon dioxide is necessary in the breathing air to obtain a protective effect? What mechanism is active in protecting the animal from the effects of anoxia?

Major F H Lewey, Medical Corps, Army of the United States Dr Crothers' question is pertinent Puppies with anoxia behave very differently from adult dogs Kabath and his co-workers found that young animals survive longer periods of anoxia than do older ones

In reply to Dr Tedeschi's question The pathologic examination of hearts was confined to cases of death from carbon monoxide Multiple hemorrhages into the heart muscle, especially the papillary muscle, were noted Such changes were reported by Klebs as far back as 1865

In reply to Dr Finesinger's question, I refer to the experience that hemoglobin becomes progressively less able to hold oxygen as carbon dioxide increases in the blood In other words, the oxygen dissociation in the blood is facilitated by increased carbon dioxide tension in the blood

MADELAINE R BROWN, M D, *Presiding*

Regular Meeting, March 15, 1945

Pathologic Changes Associated with Injury to Nerve Induced by Cold

DR D DENNY-BROWN, DR RAYMOND D ADAMS, DR CHARLES BRENNER and MISS MARGARET M DOHERTY

The results of two series of experiments were reported, both of which were carried out on cats In the first series, the sciatic nerve was exposed aseptically and a length of 1 cm packed off and frozen solid with a spray of carbon dioxide After a variable period the frozen part of the nerve was thawed by the application of a cool or tepid isotonic solution of sodium chloride On the day after the operation and at intervals thereafter the animals were examined to determine the degree of motor and sensory paralysis When the animals were killed, motor responses to faradic current applied above and below the lesion were noted The nerves were stained with a variety of histologic methods to demonstrate myelin, fat, axis-cylinders and cells

In the second series, cooled brine at a constant temperature ranging from —4 to + 3 C in various experiments was circulated through a small cylindric metal jacket surrounding a segment of sciatic nerve (20 mm) for a measured time (usually two hours) The temperature of the brine was determined by thermometers at the inflow and the outflow and the temperature of the interior of the nerve by a fine thermocouple inserted between the fasciculi of the nerve As with the first series, the animals were killed after varying periods of survival and observation and the nerves examined microscopically after suitable fixation and staining

It was found that the myelin and axis-cylinders were selectively damaged by exposure to cold, the largest fibers being the most sensitive and the smallest the least sensitive Damage to the large motor fibers and the fibers conveying sense of contact was produced by exposure to temperatures as high as + 8 C for intervals as short as thirty minutes The mildest degree of damage resembled that produced by transient ischemia, but the severe lesion differed in that destruction of myelin in the affected fibers was complete without the smallest fibers necessarily being damaged The affected myelin underwent dissolution Necrosis of whole bundles of nerve fibers occurred only after freezing Regeneration was rapid and complete in all grades of injury short of complete necrosis

DISCUSSION

CAPTAIN JAMES C WHITE (MC), U S N R I thought that my best contribution to this presentation of the effects of cold in experimental animals would be to tell of my experiences with immersion foot in the Navy In a tour of special duty to Halifax, Nova Scotia, and during the past three winters at Chelsea, Mass, I have had an opportunity to study about 100 cases of the early or late stage of these lesions which result from exposure to cold water For descriptive purposes, it is best to divide them into two distinct stages and to talk about each stage separately

In the early stage one finds lesions very similar to those described in the authors' experimental animals These consist of an inflammatory reaction, with discoloration of the skin, swelling and hyperemia There are changes in the superficial blood vessels and a progressive paralysis of the subcutaneous nerves from the ankle down to the toes Pain, burning in character, is usually present as soon as the extremities warm up and continues until the inflammatory reaction subsides (Colored lantern slides and charts were shown to illustrate these points)

In the late stage the presenting symptoms and signs are caused by contraction of fibrous tissue There is necrosis of the skin, intrinsic muscles and supporting structures of the foot, with loss of mobility and clawing of the toes The nerves have more or less regenerated, and it is very painful for the patients who have been most severely exposed to walk Lieut Comdr Shields Warren, patholo-

gist to the First Naval District, and I have studied a series of biopsy specimens obtained from such patients (Lantern slides of the photomicrographs were shown) There is a striking increase in the intercellular fibrous tissue This is limited almost entirely to the collagen, and the number of fibroblasts is not particularly increased The subcutaneous nerves are embedded in this fairly dense fibrous tissue Three months after exposure some of the nerves still show edema and a slight degree of wallerian degeneration Many of the arterioles and venules are partially to almost completely occluded as a result of the great increase of fibrous tissue within their walls Biopsy of muscles shows an easily appreciable fibrosis and atrophy of the striated fibers

From this study we have derived the impression that much of the late pain has been due to perineurial fibrosis It tends to subside after six to eight months, at which time the collagen ceases to contract There are also several other factors which deserve mention Pain is frequently a by-product of nerve regeneration Sir Wilfred Trotter has discussed this in an essay on the effects of loss of insulation (myelin) in damaged nerve fibers Such fibers have lost their normal conduction and respond only to painful stimuli, and then in an explosive, exaggerated way Owing to the infiltration of the subcutaneous tissues and intrinsic muscles with fibrous tissue, the finer arterioles are also constricted, and circulation is thereby reduced This suggests the postulate that painful metabolites are removed more slowly and are therefore an added cause of the pain which appears so consistently on walking The periarticular and peritendinous fibrosis, with added atrophy of the intrinsic muscles and ligaments which give mechanical support to the feet, is a third factor which I should like to call to your attention as important Taken all together, these factors constitute a satisfactory explanation of the long-standing pain which may be such a disabling condition in shipwrecked mariners who have been adrift for long periods in cold water

DR D DENNY-BROWN In beginning the investigation, it seemed to us that the great problems concerned with this condition centered around (1) the extreme liability to pain in the late stages and (2) the great delay in recovery of motor function The delay was satisfactorily explained by Blackwood and Russell, who showed that the muscle undergoes direct necrosis and that that presumably leads to the fibrosis of which Captain White spoke

The painful vasoneuropathy is not peculiar to this condition It is seen with various kinds of peripheral neuritis It was therefore of some general interest to find that the smallest nerve fibers, the sympathetic and pain fibers, escape The idea that hyperesthesia can result from isolation of pain sensation from other forms of sensation is not new Regeneration is not impeded, provided there is not complete necrosis

Penicillin Treatment of Neurosyphilis A Preliminary Report on Seventy Patients Followed from Four to Twelve Months DR AUGUSTUS S ROSE, DR L D TREVETT, DR J A HINDLE, DR C PROUT and DR H C SOLOMON

During the twelve months ending Feb 1, 1945, 106 patients with symptomatic neurosyphilis were treated with penicillin at the Boston Psychopathic Hospital The diagnoses for the 70 patients who have been followed for four to twelve months are as follows dementia paralytica, 49, tabes dorsalis, 6, atrophy of the optic nerve, 6, and chronic meningovascular syphilis, 9 Treatment consisted in sixty intramuscular injections of 50,000 Oxford units of penicillin (total 3,000,000 Oxford units) given concurrently or in succession with one-half the usual amount of therapeutic fever in the form of malaria or fever cabinet therapy Seven patients were treated with penicillin alone The time interval of the injections of penicillin varied, a series of cases being collected in which injections were given (1) every four hours, (2) every three hours, (3) every two hours and (4) every hour

The over-all clinical results at the time of this report show that of the 70 patients, the condition of 28 is improved, that of 37 is unchanged and that of 5 is worse

Of the 49 patients with dementia paralytica, 25 show improvement and 21 no change and 3 are worse Thirteen of the patients with dementia paralytica had been committed to state hospitals for mental disease for four months or longer The results for the remaining 36 patients are striking 24 show improvement and 11 no change, and 1 is worse Five of the 6 patients with atrophy of the optic nerve have an apparent arrest in visual loss

In a satisfactory percentage of cases the spinal fluid shows a return of the cell count and the total protein content to normal and a gradual decrease in the titer of the Kolmer-Wassermann test Study of the results for 30 patients treated by older methods reveals a comparable alteration in the spinal fluid In many of the previously untreated patients with dementia paralytica an immediate reaction consisting in increase in the cells and the protein content of the spinal fluid with intensification of symptoms was noted

Of the total of 106 patients, 7 have died Two of these demonstrated that penicillin cannot be counted on to alter beneficially the terminal phase of dementia paralytica, and the question is raised as to the advisability of using this drug in the overactive end stage

DISCUSSION

DR RAYMOND D ADAMS I know of only one previous study in which an attempt was made to evaluate the penicillin treatment of neurosyphilis That came from the clinic of Dr John Stokes, of Philadelphia, and was published in *The Journal of the American Medical Association* (Stokes, J H, and others The Action of Penicillin in Late Syphilis, **126** 73 [Sept 9] 1944) Dr Stokes and his associates observed the effects of penicillin on 180 patients with late syphilis, 122 of whom had neurosyphilis Penicillin was given intramuscularly, and in a few cases intravenously, in amounts varying from 600,000 to 4,000,000 Oxford units Improvement in the cerebrospinal fluid occurred in 70 per cent of patients, the cells disappeared, and the total protein and the titer of the Wassermann test were reduced Clinical improvement was noted in approximately 80 per cent of 40 patients with dementia paralytica, in 20 per cent of patients with tabes dorsalis and in 65 per cent of patients with meningovascular syphilis

A neurologist reading the report of Stokes desires clarification of several points It is not clear just what methods of treatment were used and what results they produced For example, it is said that some patients were given penicillin and some fever therapy, but further details were omitted It was said that clinical improvement was not always accompanied with improvement in the cerebrospinal fluid, but no attempt was made to correlate these factors It was not defined what constitutes improvement in some types of neurosyphilis For instance, how does a patient with meningovascular syphilis show improvement—by partial or complete restoration of function after a stroke or by the prevention of other vascular lesions? Of course this paper was written in the first flush of enthusiasm for the new method, and many omissions are to be expected, it serves as a stimulus to the study of penicillin in the treatment of neurosyphilis

The paper presented tonight and that of Dr Stokes indicate that the abnormalities in the cerebrospinal fluid are unquestionably influenced by penicillin therapy Dr Rose's caution in advocating the wholesale use of penicillin in treatment of dementia paralytica and in abandoning tried and proved methods is laudable Syphilis is a chronic disease, and years are required to evaluate properly any therapeutic method The methods now in existence are based on twenty or thirty years' accumulated experience So with penicillin a long period of intensive study will be necessary before its place in therapeutics can be assigned

It is well to remind persons not working in this field of some of the major difficulties encountered in the treatment of neurosyphilis Older methods of treatment, which include the use of trivalent arsenicals and bismuth, fever and tryparsamide, are fairly effective When they are used in cases of the latent and asymptomatic disease, the development of serious late forms of neurosyphilis can usually be prevented Some of the difficulties encountered in the application of existing

methods may be noted 1 Most patients who come to a neurosyphilis clinic did not know before that they had syphilis, and therefore they have never been treated for the disease Dr Merritt and I looked over our rather large material at the Boston City Hospital and found that about 80 per cent of our patients did not know they had syphilis and had never had any treatment until neurologic symptoms developed The remainder had received only very inadequate treatment This explains why present therapeutic methods have not significantly reduced the incidence of neurosyphilis This difficulty actually reduces itself to the problem of case finding The only solution lies in the routine serologic testing of blood for syphilitic reagin, in making lumbar punctures in all cases of latent syphilis and in treating the patient until the cerebrospinal fluid is normal

2 Existent methods of treatment require time and the cooperation of the patient He must come to the clinic week after week In the clientele of a large city hospital, which includes many itinerants, psychopaths and the like, it is difficult, even with the assistance of a social worker, to maintain faithful attendance at the clinic and thus to provide adequate treatment Of 250 of our patients with asymptomatic syphilis, only 100 received enough treatment to bring about a serologic reversal of the cerebrospinal fluid

3 Older methods of treatment when applied intensively over a short period and fever therapy carry some risk, especially for elderly people with complicating diseases

For these reasons, syphilologists seek new drugs which are safe and quick acting

The investigation which Dr Rose and his association have presented is a conscientious and sober evaluation of the treatment of dementia paralytica with penicillin In a way, it is unfortunate that fever therapy, even in reduced amounts, had to be given with the penicillin treatment, but the reasons are obvious What is needed, of course, are many more patients with asymptomatic neurosyphilis and early dementia paralytica treated with penicillin alone and observed carefully for a long period

I wish to ask several questions 1 Have the authors determined the concentration of penicillin in the cerebrospinal fluid? Keefer and Anderson showed that penicillin does not enter the cerebrospinal fluid from the blood stream and suggested that the drug has to be given intrathecally if it is to be effective Other workers pointed out that in cases of meningitis, in which exudation occurs, penicillin reaches the cerebrospinal fluid in sizable quantities Is it necessary to have a high level to achieve a good result? If so, will it become necessary to give the drug intrathecally?

I know of Dr Solomon's reluctance to admit that any real Herxheimer reaction occurs in the cerebrospinal fluid How does he regard the intensification of symptoms mentioned in this report? Is there any risk in injecting a large amount of penicillin into an untreated patient? Is there any danger of producing transverse myelitis or a vascular lesion?

Dr William R Hill My associates and I have used penicillin at the Massachusetts General Hospital since September 1943 in treatment of patients with primary and secondary syphilis, all of whom had active lesions from which spirochetes morphologically consistent with Treponema pallidum were obtained Our method of treating these patients has been to hospitalize them and treat them with intramuscular injections of 20,000 units every three hours for seven and a half days, for a total of 1,200,000 units There was one interesting observation Four of the patients experienced a pronounced Herxheimer reaction after the second dose They had a temperature of 103 and 104 F and suffered severe pains in the back and chills We continued, however, to give penicillin at regular intervals of three hours, and the symptoms subsided, without residuals We believe there is no danger in continuing penicillin therapy under these conditions The Wassermann reaction of the blood became negative in thirty to seventy days in the majority of cases, and active lesions resolved in three weeks We studied the spinal fluids of all our patients before treatment and found them to be normal In a recent lecture

Moore stated that 20 per cent of a large group of patients with early infectious syphilis had a serologic or clinical relapse within the first year Now a plan is being set up to increase the effectiveness of penicillin with a rapid course of treatments with arsenicals or fever

DR HARRY C SOLOMON First, I shall try to answer Dr Adams' question I suppose I am a bit stubborn about the Herxheimer reaction The phenomenon may be due to the killing of spirochetes, but there may be something else involved Some form of exacerbation is present in the central nervous system of these patients The cell count rises characteristically in all cases in which this treatment is used

The question whether penicillin alone would be adequate in treating dementia paralytica is not answerable at this time, Dr Hill has pointed out that in cases of early syphilis in which penicillin is of proved value relapses are not as infrequent as one would like At any rate, there are a number of clinics where the drug is being used as the only treatment, and their results will elucidate that point without our aid Hence, we have kept on with what we should ordinarily consider an inadequate course of fever therapy in conjunction with the use of penicillin Four or five febrile bouts do not take much out of the patient They do not leave him "washed out" and weak They can be given at the same time that the penicillin therapy is being carried on The general evidence is that penicillin becomes more effective with each degree of rise in body temperature Whether with fever the penicillin is broken down or eliminated so rapidly that an adequate blood level is not maintained we do not know

Whether penicillin should be given intrathecally has been considered We decided to get as much information as possible about the intramuscular method before trying the intraspinal route Some have used the intrathecal method, but it has not been proved very definitely that it is more beneficial

There is one observation of mine that may not be accurate Dr Rose has presented the statistical data on the effects of treatment and has pointed out the dramatic improvement of patients with dementia paralytica when they receive ten or twelve treatments of fever This dramatic, sudden improvement seems to be less frequent with penicillin therapy I think we have seen no resulting hallucinations, such as one finds in the treatment of dementia paralytica with malarial fever alone If this method of induction of small amounts of fever with malaria combined with penicillin therapy is as effective as a long course of fever treatments followed by a long course of chemotherapy, then it is a great advance At the present time it looks as though we were getting very good results We still have many variations to consider We have been using 3,000,000 units as the total dose Should we use a different amount, say 6,000,000? What about the period between treatments—one, two, three or six hours? Should penicillin therapy be combined with chemotherapy? Should intrathecal injections be given? Should one give longer courses of fever and penicillin therapy, with the expectation of getting better results than with either method alone? These are some of the aspects of the problem which are before us

To answer Dr Adams' question as to the penicillin in the cerebrospinal fluid We have not set up requirements for the recovery of penicillin The procedure is not difficult but is somewhat complicated Such a determination has not been made We do not have any information on the matter, nor does any one else One does not have to find the penicillin in the spinal fluid to prove that the drug is useful The amount of arsenic in the cerebrospinal fluid is not related to its effectiveness So we are not unduly concerned about its determination in the fluid

DR ALFRED HAUPTMANN I have only one question Can Dr Rose tell us about the changes seen at autopsy in the brains of the 7 patients who died? I am especially interested to know whether there were changes from the histologic picture of dementia paralytica to that of meningovascular syphilis Viennese investigators found such changes after treatment with malaria This means a change from an ectodermal to a mesodermal reaction

DR AUGUSTUS S ROSE We believe that this sudden increase in cells and protein and the temporary intensification of symptoms occur only in cases in which the patient had not received recent antisyphilitic therapy It does not occur during the second course of penicillin treatments These facts indicate that the reaction has something to do with the activity of the disease

DR JAMES B AYER I was particularly impressed with the success in treatment of primary atrophy of the optic nerve, for this serious condition has not in my experience yielded to any other form of treatment

With reference to the cell count as indicative of pathologic activity, I would remind you of an early article by Dr Solomon in which he stated that cells were sparsely present in the spinal fluid and yet at autopsy many cells were found enmeshed in the subarachnoid space

DR AUGUSTUS S ROSE We do not have data regarding the type cell which is liberated The intensification of symptoms argues for a temporary increase in the inflammatory process rather than a flushing of the perivascular spaces of the cells

The 6 cases of atrophy of the optic nerve were clearcut All the patients received injections of penicillin and treatments in the fever cabinet All had determinations of the visual fields and visual acuity at frequent intervals One showed progression of visual loss In 2 of the remaining 5 patients vision seems to have improved Their visual fields are questionably wider There may be some improvement in acuity We realize that partially blind patients often have subjective improvement while under active treatment, so we make no claims In all 6 cases the atrophy of the optic nerve is apparently of the typical syphilitic primary form In none was there evidence suggesting atrophy of the optic nerve due to basilar meningitis A recent preliminary report from another clinic participating in the investigation of the Office of Scientific Research and Development indicates that their results in cases of primary atrophy of the optic nerve are approximately the same

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ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M D, *President*

Regular Meeting, March 1, 1945

Spain as the Cradle of Psychiatry DR PETER BASSOE, Chicago†

It is generally believed that there was no humane treatment of the insane in Europe until Pinel broke their chains, one hundred and fifty years ago However, Pinel himself pointed to the fact that in Spain numerous good institutions, humanely administered, were founded in the fifteenth century This is amply confirmed by German medical historians Thus, A Schmitz, writing in 1884, stated "Not Pinel, but physicians in Valencia in 1409 were the first to remove chains and institute moral treatment" Ullersperger, in his book on early Spanish psychiatry (Die Geschichte der Psychologie und der Psychiatrik in Spanien von den altesten Zeiten bis zur Gegenewart verfasst, Wurzburg, A Stuber, 1871), says that the cradle of psychiatry was in Spain and that "earlier than other nations, the Spaniards constructed convenient and appropriate buildings, the first real hospitals for the insane in the world" However, a recent Spanish writer, Gorriz, makes the statement that the first to break the chains of the insane was Cælius Aurelianus, who lived in Carthage in the second century A D As a matter of fact, the stimulus to the kind treatment of the insane in Spain came from the Arabs, who, again, had received theirs from the ancient Greeks, whose writings they copied in profusion and

† Dr Bassoe died Nov 5, 1945

furnished to libraries in North Africa and the then Moorish Spain While Christians in Europe generally looked on the insane as possessed of demons, the Mohammedans, not stressing the devil, treated them as sick people Thus, in the thirteenth century patients in the asylum at Cairo were soothed by harmonious music and entertained by story tellers, dancing and light comedies The more important early Spanish psychiatric literature was reviewed, as well as the writings of the philosopher-physician Maimonides and the psychologist Luis Vives and those by and about the novelist Cervantes, and their psychiatric implications

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DISCUSSION

DR FRANZ ALEXANDER, Chicago In this most interesting, scholarly essay, Dr Bassoe has come to a convincing conclusion concerning the claim expressed by several authors that Spain, and not France, should be considered the cradle of modern psychiatry By a critical study of historical sources, he has confirmed the fact that the humanization of the treatment of psychotic persons started earlier in Spain than in other European countries and that Pinel, by removing the chains from the insane, only repeated what more than three hundred years before had been accomplished in Spain On the other hand, together with other cultural achievements of Spain, this progressive attitude toward the mentally sick, as well as some valid descriptions of psychotic conditions, became lost to the rest of Europe, and only after their rediscovery in other countries did these achievements exert an influence on the development of psychiatric thought A glance at the general contours of European history furnishes the answer to the question why early attainments of Spanish culture did not further develop in Spain itself and could exert influence on the shaping of European destiny only after they were transplanted to other countries

From the eleventh century until the death of Philip II, in 1598, Spain was one of the focal points of European development During these centuries she was the standard bearer of Christianity against Mohammedan expansion With the victory of Lepanto, Philip II conclusively sealed the destiny of Islam in Western Europe At the same time, Spain became the moving spirit of the counterreformation In its fanatic defense, she became the leading European power, and the militant church, in combining feudal romantic chivalry with fanatic Catholic devotion, became a grandiose historical force

Spain in the sixteenth century was the most powerful remaining citadel of medieval Catholicism in Europe and gave to its spirit in the persons of Loyola, Philip II, Saint Theresa, El Greco and Cervantes everlasting expression In the counterreformation, led by Spain, medievalism made a last and tragic dying effort to stem the tide of the new era Eventually, the spirit of romantic chivalry, mysticism, faith and passionate devotion had to yield to the victorious onslaught of modern rationalism The spectacular rise and rapid downfall of Spanish hegemony over Europe belong to the most dramatic periods of history Spain owes much of her greatness, but also her downfall, to her leadership in the counter-reformation Her economic, political and spiritual disintegration had begun already under Philip II's reign and reached rapid completion under his two successors

Historians of the nineteenth century often speak of the isolation of Spain within Europe Ullersperger, one of Dr Bassoe's sources, quotes a French historian in saying that "Spain is the least known of all countries of Europe, some islands of Oceania are better and more completely explored" These historians obviously refer to Spain after the seventeenth century *Sic transit gloria mundi!* Spain, which in the sixteenth century made such a deep imprint on European customs, social forms, dress and also spiritual outlook, soon became the "forgotten man" of Europe, together with many of her cultural contributions Early achievements in psychiatric practice and knowledge are only one of the many treasures buried under the ruins of modern Spain

Spain's tragedy was that at the dawn of the modern era, unlike England, she failed to ride the "wave of the future" As a result, the first country to benefit from colonial expansion—which itself was the fruit of the adventurous awakening spirit of the Renaissance—she was also the first of the new national states to lose her influence in the European concert of powers The hidalgo, with his adventurous inclinations, was possibly an able conqueror, but with his anachronistic ideology he was certainly not so well prepared to become a successful colonizer as the Dutch or the British trader The genius of Spain was not in this field Cervantes himself, on the basis of his pitiful record as a public administrator, was unable to obtain a governmental job in the Spanish colonies and thus was forced to continue his unsuccessful efforts to earn his living from writing While Spain's early psychiatric achievements, in the technical sense, were lost, to be excavated five hundred years later as curiosities by modern medical historians, Cervantes' contribution to the knowledge of man's nature survived in a most dynamic fashion *Don Quixote's* singular appeal to the young and old of all nations through three hundred years has been the topic of innumerable publications, only equaled by those about *Hamlet,* sharing with the latter the first place as the most profound portrayal of the universal conflicts of man A short discussion cannot do justice to this masterpiece, the first psychologic novel of literature, but I should like to call attention to a few outstanding points

It is customary to consider the story of *Don Quixote* as a masterful parody of contemporary Spanish society, particularly of the deteriorating hidalgo, the exponent of the small nobility, who no longer had a place in changing society and lived a shadow existence on the memories of past glory Cervantes' father, Rodriquez, was a typical case, constantly fighting against his creditors by insisting on the privilege of a hidalgo not to be jailed for failing to pay his debts Cervantes himself fought against the Mohammedans in the service of the king and lost the use of his left hand from wounds received in the battle of Lepanto In literary criticism, as in every other field, there are the so-called realists, who can see only the obvious and are insensitive to those overtones which make the difference between ordinary literary production and a masterpiece It is, of course, obvious that *Don Quixote's* tragicomedy is the symbolization of the dying Spanish culture in the sixteenth century The perceptive eyes of the great writer foresaw in a sense the fate of a nation which, like its grandiose exponent Don Quixote de la Mancha, turned its face toward the past and in vain tried to keep alive the feudal ideology of romantic chivalry and militant religion, which, no matter how noble and inspiring, were doomed and had to yield their place to the new realistic orientation However, the story of *Don Quixote* is more than contemporary satire It is no secret with whom Cervantes' heart is, all his sympathy is with Don Quixote, the foolish knight, who, in spite of all his insanity, becomes the martyr of his idealism and the symbol of the higher strivings of man, while reason is represented by the faithful, but so utterly banal, Sancho Panza However, reason survives and Don Quixote dies, and all feel sad and poorer after his departure This universal effect on all readers shows that the tragedy of Don Quixote is not merely the local, time and space bound, tragedy of Spain, but is that of all man To turn away from frustrating and drab reality by regressing to the colorful imagery of the past is a fundamental psychodynamic principle This regressive trend, in different degrees, is present in every healthy or sick person Psychotic symptoms do not follow psychologic principles different from normal processes There is no special physiology for healthy and another for pathologic processes of the body, and, similarly, there are not two kinds of psychology, one valid for the healthy and one for the neurotic and psychotic mind The basic principles are the same in psychology and in psychopathology It is no accident that a Spaniard of the sixteenth century was the first to make the escape from the unbearable present into imagery of the past the central theme of a novel and to understand the paramount significance of regression in psychosis Shakespeare and Cervantes died in the same year Both anticipated science by three hundred years in bringing nearer to one's understanding

the baffling irrationality of the disturbed mind Shakespeare succeeded in awaking one's compassion for the compulsive doubter, whose scruples and indecision provoke in the ordinary man—and even in the physician—nothing but impatience and irritation Cervantes' achievement from the psychiatric point of view is even greater, he succeeded in awaking one's sympathy and empathy for the raving paranoiac by his instinctive understanding of his psychosis as a regressive retreat from reality into phantasy For the psychiatrist, it is of special interest to note that Don Quixote and Sancho Panza are, like Don Juan and Leporello, complementary figures, personifying the two aspects of one and the same person Most psychotic persons, apart from their autistic attitude, retain a certain amount of practical sense, which enables them to move around in the world They live a double existence, retaining a tenuous practical relationship to the world, overshadowed by the self-created world of phantasy Sancho Panza is the personification of the subordinated reason, helping his master, by taking care of his practical needs, to live by his folly Only together, in their fascinating symbiosis, do Don Quixote and Sancho Panza—really one person—give a faithful picture of the paranoiac personality

In a sense, psychosis and psychoneurosis are the most human of all diseases Every animal can have stomach or heart trouble, but only in extremely rudimentary form a neurosis or psychosis Phantasy, the faculty of imagining, is the basis of thinking which enables man to master his environment better than any other living organism In psychosis this faculty is abused, not for mastering but for escaping from the reality which has overpowered the mentally sick Perhaps this is the main, but hidden, reason that one cannot forgive the psychotic person Because he abuses the most distinctive faculty of man, society has stigmatized him for centuries Cervantes made a good case, in fact, the best possible case, for the psychotic person, demonstrating so effectively the extenuating circumstances in his favor The ideals and principles of Don Quixote were lofty indeed, and, in a way, one cannot help admiring his tenacity in trying to live up to them One regrets that life does not allow him to live the exemplary life of a knight errant It is difficult to laugh at and despise him—the most one can say is that he was not for this world—he was too good for it Is this not true also for many patients? Understanding the psychotic personality is the way of overcoming the stigma of mental disease Perhaps it is not a coincidence that Spain, the first country to remove the chains from the psychotic patient, produced the man who was the first to understand him

Behavior Problems in an Army Service Forces Training Center CAPTAIN LEO A KAPLAN, Medical Corps, Army of the United States

The problems of behavior disorders in an Army Service Forces training center were considered from the standpoint of their importance not only for the present but for the future I refer particularly to simple adult maladjustment, mental deficiencies, chronic alcoholism, constitutional psychopathic states and malingering As psychiatrists we have long recognized the almost hopeless and ever increasing burden persons suffering from these disorders place on themselves, on their families and on society in general My assignment in the service has placed me in a position to study these persons over a period of fourteen months in an Army Service Forces training center

The psychopaths more or less retain their civilian pattern of behavior in the Army and as a group are incapable of attaining satisfactory adjustment It has become apparent that all efforts at their rehabilitation are unsuccessful Rehabilitation has had a fair degree of success with persons who are recidivists but whose past personality is free from psychopathic tendencies (Examples of various bizarre behavior problems were discussed, and the histories of some malingerers were given)

It is the general consensus that the majority of guardhouse prisoners, i e, the psychopathic, the alcoholic and other mentally ill persons, should never have been inducted into the military service On the other hand, to reject these persons or to return them to civilian life obviously creates resentment and poor morale in the

soldier who is conscientious and willing to make sacrifices Most important is the ultimate effect on society The old proverbial expression "survival of the fittest" becomes a paradox The mentally and physically adequate youth of the nation are becoming invalids by the hundreds of thousands, whereas remaining behind are the psychopathic, the alcoholic and the other mentally unfit, who will continue to display their asocial and antisocial behavior—economic burdens to society and financial drains on the Government

It is my personal opinion that it has been an error in judgment not to consider this fundamental proverbial saying, "survival of the fittest" The great postwar problem will be the same old question, only ever increased, "What shall we do with the psychopath?"

DISCUSSION

CAPT CHARLES O STURDEVANT, Medical Corps, Army of the United States When the psychiatrist is confronted with the particular group under discussion, the problem of making a diagnosis is often difficult For a long time I have been concerned in the making of any psychiatric diagnosis and have tried to hew to a rather rigid line in my discussion of this subject with other medical officers As a member of many disposition boards, it has fallen to my lot to explain some of these diagnoses to other officers I have felt that we psychiatrists are in need of a different sort of terminology We are calling many things "psychoneurosis" in the Army as a matter of convenience, and I think it is true also in designating the psychopathic personality I am sure that I have made mistakes of that kind in order to get rid of a man who was giving trouble within the command At one time I suggested putting all such men in one company for special duty and training, as Dr Kaplan indicated has been done in other countries In England such groups are called "pioneer battalions," and they perform labor, often in combat areas

My initial experience with the problem came in connection with Selective Service, when Dr Harry Stack Sullivan visited the West Coast to set up standards for selection Then it seemed that 25 per cent of the rejections should be for psychiatric reasons My associates and I attempted to follow the standards, rejecting 25 per cent, but soon local directives stated that there were too many psychiatric rejectees, and the number dropped to 10 per cent I think the problem of demand often determines the role of the psychiatrist in many induction stations

In discussing the psychopathic soldier, the question was raised, "What about the French Foreign Legion, an army composed of psychopaths, distinguished fighters, and considered to be very brave?" Dr Sullivan's comment was that perhaps we should be able to get some of these egocentric fellows to the battle line but there would be so much trouble involved that the whole army would be worn out before they began to fight This certainly has been my experience

Another factor concerned with this group is that the psychopathic soldier is extremely hard on the morale of any unit The medical officer, and the psychiatrist in particular, is often confronted with the problem of discharging some person whom he feels is definitely psychopathic The social history will support his view, but the commanding officer, when confronted with this decision, may object because he fears it will encourage others to seek discharge I remember an instance in which regulations of the War Department permitted certain men of a certain age to leave the service After a month or two the order was rescinded, and for several months afterward there was an epidemic of certain types of "discharge blues"

The problem of psychoneurosis in the Army is probably best handled through correct orientation and early evaluation, as is done in replacement training centers The technics vary a great deal Recently I have had an opportunity to review various plans in use and have found that psychiatric planning is rather individual In one place they have set up what is called an advisory system In another camp they may give orientation lectures, another has a mental hygiene director who is responsible to the commanding officer of the camp All these plans seem to work rather effectively One of the most useful programs in military neuropsychiatry is that of the division psychiatrist His men are different from Dr Kaplan's The

division psychiatrist works with psychopaths, orienting them, assisting the command in classification and assignment, trying to teach them what psychologic adjustment in the Army should be By the time they arrive at a port of embarkation these men are pretty well known to the psychiatrist He knows whom he wishes to take, who he feels can tolerate the rigors of combat and who may have difficulty in the future Perhaps he can carry one or more of the psychopaths into battle

Cross Section Perspectives of Current Psychiatric Cases at the Juvenile Court DR SAM I STEIN, Chicago

Among personality problems of children is that complex known as delinquency This is a legal, rather than a psychiatric, classification This and other behavioral disturbances occurring in children are distinguished from those of adults mainly for academic, rather than clinical, reasons Basically, no causal or etiologic separation can be made, for differences in child and adult personality problems are mainly in the outward manifestations or the visible and invisible symptomatology A cross section appraisal of delinquency could be substituted for a cross section appraisal of seemingly different psychiatric segments Correct answers in diagnosis and therapy for juvenile delinquency should have universal application in psychiatry's entire sphere of interest and competence

Twenty-two cases are cited which are truly representative of various types encountered among the 1,000 or more children studied annually Ample identifying material is given to place the patient in the most appropriate of three broad causal categories somatogenic, or disturbances due to visible or invisible lesions of tissue structure, psychogenic, or disturbances due to intrinsic inhibition or emotional immatureness, and sociogenic, or disturbances due to poor or improper conditioning Accordingly, this representative psychiatric problem is not covered by the wide base of psychosomatic medicine but is included in the still broader field of socio-psychosomatic medicine

Just as in other medical disciplines, wherever feasible, treatment should be directed toward the cause of the ailment and symptomatic manipulations resorted to only when there is no practicable alternative The human problem today is beyond the stage at which preventive measures alone will give needed results in the time available for interrupting the natural process of morbid psychogenesis Specified features of treatment appropriate to each major causal category are discussed Emphasis is placed on the extreme need for testing the probable specific of psychotherapy, which is described in the text as an attribute of energy The idea of such a phenomenon is supported by Sherrington

Men speak of needing more freedom in the social scheme Actually, man is unprepared even to legislate freedom until he has freed himself of his emotional immatureness, which implies intrinsic insecurity, irrational aggression and selffish, subjective motivations and which causes him, through seemingly indisputable rationalizations, to wittingly or unwittingly enslave others in the widest range of manners, from that of fondly infantilizing a child to that of ruthlessly forcing another into compulsory servitude Psychiatry is seriously in need of the "specifics or the common denominators" of psychotherapy, not only to help resolve the problems of delinquency but, in view of the unpredictable state of human affairs, to assist in waging successful, psychologic peacefare

Book Reviews

Personality Factors in Counseling By Charles A Curran, Ph D Price, $4 Pp 287 New York Grune & Stratton, Inc, 1945

This book is the work of a Catholic clergyman who has had psychologic training Bishop Ready, of Columbus, Ohio, has written a brief preface, and Prof Carl R Rogers, of the University of Chicago, gives an interesting introduction to the subject of counseling Dr Curran has attempted to "analyze the inter-related functions and attitudes revealed in the personality during the process of adjustment" He states that definite therapeutic gains can be achieved with the technic of "non-directive" counseling, in which the counselor acts as a passive agent and makes no attempt to direct the client toward goals

The greater part of this book is devoted to an elaborate and detailed statistical analysis of the case report of a single patient Twenty interviews were phonographically recorded, and typescripts thus obtained were independently analyzed by several psychologists, with surprisingly consistent results The relationship between client and counselor was carefully controlled in an attempt to place on the client the entire responsibility for the solution of his problems Client attitudes were rated by means of (1) interview content analyses, in which arbitrarily chosen categories of negative and positive emotional responses and chance responses were tabulated by three observers, and (2) problem-solving analyses, in which a list of individual problems facing the client was made up at the start of the interviews and followed through to the last interview in order to evaluate the function of insight in the process of therapy The relations between 1 and 2 were plotted diagramatically by means of insight evaluation charts

In his summary, Dr Curran agrees essentially with the earlier results of Rogers, Snyder and others and states that "the ability to make independent choices and put them into practice brings the client much greater self-confidence and happiness and he no longer feels that he needs help"

The last part of the book, entitled "Implications for a Philosophy of Personality," deals with the possible application of counseling to individual and social betterment

This book is a valuable, accurate and stimulating work and should serve to promote interest in the application of objective methods of research to psychologic interviewing technics Dr Curran has carefully presented and analyzed his material and has a wide knowledge of academic psychology The applicability of this method to psychotherapy, however, is subject to questioning, in the reviewer's opinion The approach to the client is of necessity on a very superficial level, no attempt being made to investigate the unconscious factors underlying the neurotic symptoms The author carefully avoids more than passing reference to freudian or other psychotherapeutic concepts in his dscussion of the benefits of counseling The term "non-directive" may be disputed also, in that any interview situation implies considerable rapport between subject and examiner and it is practically impossible to avoid "directing" the client along certain lines of thought The author's assumption that "the ability to solve his own problems lies within each individual" and is a function of the "responsible dignity of human nature" may be valid in cases of simple social maladjustment, such as that of Alfred analyzed in this book, but it has little scientific value when one is dealing with treatment of the psychoneuroses, which may require many months of "active" psychotherapy by trained psychiatrists before any improvement occurs

Unfortunately, a case history prior to the interview is not given, so that the medical reader is unable to make his own judgment or diagnosis and hence cannot evaluate the results of the interview "therapy"

This book is recommended to persons interested in objective methods of psychologic research applied to the special field of counseling It is also of interest to psychiatrists in that it offers a possible method of statistical evaluation of the "productions" of patients, the interpretation of which heretofore has been left largely to individual judgment

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ASSOCIATED MOVEMENTS IN THE OCULOMOTOR AND FACIAL MUSCLES

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ABNORMAL motor phenomena belonging—generally speaking—to the vast group of hyperkineses do occur in the oculomotor muscles after incomplete recovery from a third nerve palsy They constitute, as Bielschowsky [1] rightly said, "a problem of great biologic interest" But this difficult and fascinating problem has been much neglected in the neurologic literature The symptomatology and pathogenesis of abnormal motor phenomena in the facial muscles after incomplete recovery from facial nerve palsy have been widely discussed by neurologists. But there is little in the neurologic literature on the subject of similar movements after oculomotor palsy To Dejerine [2] it seemed that abnormal movements occur only after a seventh nerve palsy, and in no other instance Leading contemporary neurologists, such as Harris [3] and Kramer,[4] have expressed the same view The latter said "It is remarkable that contractures and associated movements are observed in the region of the facial nerve and not in the region of any other nerve" Oppenheim,[5] in his textbook, devotes but four lines, in small print, to the subject of abnormal movements following a third nerve palsy No mention is made of this subject in the textbooks of Wilson, Brain, Grinker, Wechsler, Nielsen, Bing and others, nor is it referred to in the most

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1 Bielschowsky, A Die Motilitatsstorungen der Augen, in Graefe, A, and Saemisch, T Handbuch der gesamten Augenheilkunde, ed 2, Leipzig, Wilhelm Engelmann, 1910, vol 8, pt 2, chap 9, p 196

2 Dejerine, J Semiologie des affections du systeme nerveux, Paris, Masson & Cie, 1926, p 583

3 Harris W Neuritis and Neuralgia, London, Oxford University Press, 1926, p 364, Tremor, Ataxy and Spasm, Lancet 2 1145, 1934

4 Kramer, F, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 4, p 350

5 Oppenheim, H Lehrbuch der Nervenkrankheiten, ed 7, Berlin, S Karger, 1923, p 737

(See legend on opposite page)

Fig 1 (case 1) —Patient (*a*) looking straight ahead, (*b*) trying to open his eyes wide, (*c*) looking to the right, (*d*) with the right eye passively closed, (*e*) looking downward, (*f*) looking upward, (*g*) looking horizontally to the left, (*h*) looking to the left and downward

extensive treatise on neurologic examination in existence, that of Sahli Ophthalmologists have written extensively on this subject, but their work is predominantly descriptive They have developed a hypothesis on the pathogenesis of these phenomena which has been widely accepted also by neurologists

The primary object of the present study is a critical analysis of this hypothesis, based on the personal observation of 4 cases

REPORT OF CASES

CASE 1.—A man aged 23 sustained a skull fracture and severe injury to the brain in an automobile accident He underwent four neurologic examinations, twenty-one, thirty, thirty-seven and forty-five months, respectively, after the accident The same condition was found each time, namely, left-sided oculomotor palsy, as the only sequela of the injury There were no other neurologic changes He had no postcommotional cerebral syndrome, no double vision His only complaint was the cosmetic effect of his oculomotor palsy

On examination he showed an incomplete palsy of the left oculomotor nerve From his statement it was concluded that this palsy had been complete after the injury and had slowly improved The left eye was in abduction of about 20 degrees The upward and downward movements of the eye were greatly limited The adduction was slightly better, and the abduction was normal The left pupil was twice the size of the right and showed no reaction to light and no reaction on inward, outward or downward movement of the eye, but it contracted slightly on upward movement No consensual pupillary reaction to light was obtained from right to left, but it was present from left to right When he looked straight ahead (fig 1*a*), pronounced ptosis and an abducent position of the left eye were noted The orbicularis oculi muscle was normal When asked to open his eyes wide (fig 1*b*), he performed the movement hesitatingly, and despite maximal effort and strong innervation of the frontal muscle he was able to lift his left lid only slightly, the eyeball moved simultaneously very slightly inward or remained immobile On his looking to the right (fig 1*c*), the left eyeball did not assume the full extreme position, as did the right The left upper lid rose and assumed a position higher than the right one When the patient looked straight ahead with the right eye passively closed by the fingers of the examiner (fig 1*d*), the left eye moved inward, and the left lid rose It rose higher the more he fixated an object The moment the examiner removed his fingers and the patient opened his right eye, his left lid again drooped and the eyeball assumed a position of abduction When, with his right eye passively closed, the patient was asked to look to the left, the left lid drooped, and it rose again when the patient fixated an object in front of him No lifting of the left lid occurred when the patient was asked to fixate a distant object with both eyes open When he looked downward (fig 1*e*), there were a very slight downward movement of the left eyeball, a slight movement inward, a distinct rotation of the eye clockwise and a conspicuous elevation of the upper lid When he looked upward (fig 1*f*), there were a slight upward movement of the eyeball, a pronounced inward movement—much more than on looking downward—and a marked elevation of the upper lid When the patient looked horizontally to the left, the ptosis of the left lid became complete (fig 1*g*), but when he looked to the left and downward, the left upper lid rose automatically (fig 1*h*) On his looking to the left and upward, the eye remained in the same horizontal position, and the ptosis remained as in the position of rest

On strong convergence a slight inward movement of the left eye occurred, with elevation of the left lid, but both movements were less marked than when he was asked to move the left eye inward On closing of the eye, Bell's phenomenon was present on both sides

CASE 2—A 7 year old boy fell thirty-five days previous to the neurologic examination and suffered a fracture of the occipital bone, two days later pneumococcic meningitis developed After two more days left-sided palsy of the

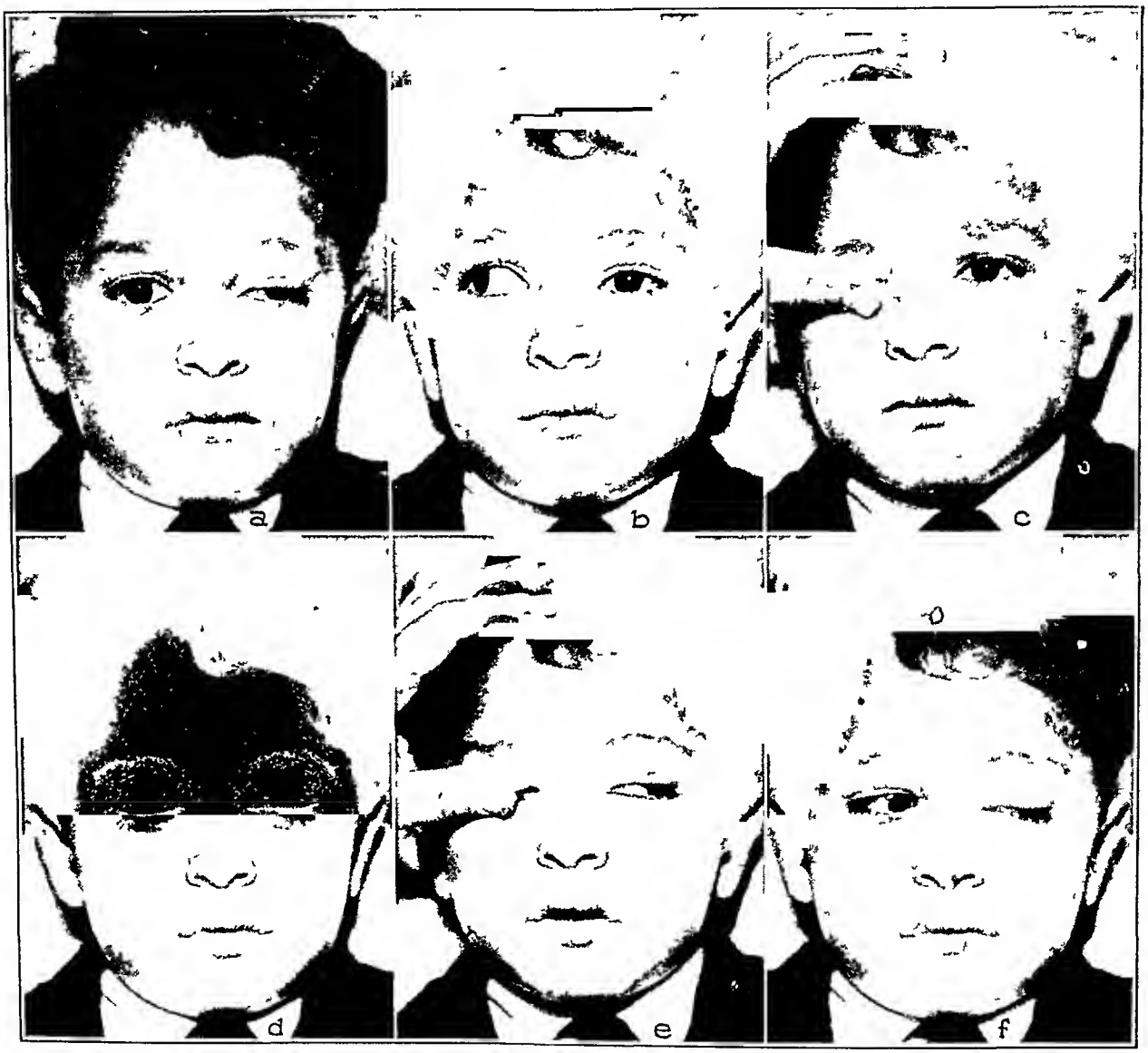

Fig 2 (case 2) —Patient (*a*) looking straight ahead, (*b*) looking to the right, (*c*) with the right eye passively closed, (*d*) looking downward, (*e*) with the right eye passively closed, looking to the left, (*f*) looking horizontally to the left

third nerve with complete ptosis was noticed He had no complaints referable to the cerebral injury, and the neuropathologic changes were confined to the left oculomotor nerve The patient showed an incomplete left-sided palsy of the third nerve, with mild ptosis and an abducent position of the eye (fig 2 *a*) Voluntarily, on great effort, he was able to lift the upper left lid slightly The pupils were normal On his looking to the right (fig 2 *b*), the left eyeball followed only as far

as the midline and the left lid rose but not so high as the right When the right eye was passively closed by the fingers of the examiner, the left eyeball moved inward and the left eyelid upward (fig 2 *c*) On his looking downward (fig 2 *d*), the left upper lid moved downward in a normal fashion When, with the right eye remaining passively closed, the patient was asked to look to the left, there

(See legend on opposite page)

was no elevation of the upper left lid, and the ptosis remained as it was in the position of rest (fig 2 *e*) On his looking horizontally to the left, the ptosis became more marked (fig 2 *f*) After one year the patient was reexamined He showed complete recovery, and no associated movements or any other pathologic changes relative to the left eye could be demonstrated The recovery took place without any therapy, exercise or other measure

CASE 3.—A 58 year old man had tabes dorsalis and incomplete paralysis of the left third nerve. The first symptoms of this paralysis dated ten years back. When the patient was at rest and looked straight ahead, the ptosis was complete (fig. 3 *a*). On great effort he was able to lift his left eyelid slightly (fig. 3 *b*) but only for a short time. On looking to the right, he demonstrated a partial paralysis of the

Fig. 3 (case 3).—Patient (*a*) looking straight ahead, (*b*) trying to open his eyes wide, (*c*) looking to the right, (*d*) with the right eye passively closed, (*e*) looking downward, (*f*) fixating an object below the horizontal level, (*g*) fixating an object at the horizontal level, (*h*) looking upward, (*i*) looking to the left and horizontally, (*j*) looking to the left and upward.

left rectus internus muscle, and the left eyelid rose automatically to a maximal degree (fig. 3 *c*). When the right eye was passively closed by the finger of the examiner and the patient stared straight ahead, the left eyelid rose (fig. 3 *d*). When

he looked downward (fig 3 *e*) or when he fixated an object below the horizontal level (3 *f*), the left eyelid followed the downward movement of the eye in a normal fashion, even more than did the right eyelid But when the patient was asked to fixate an object at the horizontal level, the left eyelid rose automatically to a considerable extent (fig 3 *g*) When he looked upward, the left eye hardly participated but moved slightly inward, while the left eyelid moved extensively upward (fig 3 *h*) When he was asked to look to the left and horizontally, the ptosis

Fig 4 (case 4) —Patient (*a*) looking straight ahead, (*b*) trying to open the eyes wide, (*c*) looking to the right, (*d*) fixating an object below the horizontal level, (*e*) fixating an object at the horizontal level, (*f*) looking upward

remained unchanged (fig 3 *i*), but when he looked to the left and upward (fig 3 *j*), the left eyeball hardly followed this upward movement, whereas the left eyelid rose automatically

Case 4 —A 40 year old woman had a specific infection, first diagnosed three years before the present examination At that time a lesion of the left oculomotor

nerve was noted At the present examination she showed an incomplete palsy of the left oculomotor nerve with ptosis (fig 4 *a*) According to her statement, this ptosis was at first complete but since had slowly diminished On strong exertion she was able to correct this ptosis (fig 4 *b*) and could lift her left lid, but only for a few seconds The left lid then moved downward to the former position When she looked toward the right, there was an automatic elevation of the left upper lid (fig 4 *c*) There was no elevation of the upper lid on looking downward, the left upper lid following the downward movement of the eyeballs in a normal fashion No elevation of the upper lid resulted when the patient was asked to fixate an object below the horizontal level (fig 4 *d*), however, when she was trying to converge on an object placed at the level of the eyes, the left lid rose, although the adduction of the left eye was very deficient (fig 4 *e*) On looking upward, there was almost no upward movement of the eyeball but, rather, an automatic movement of the eyeball inward with elevation of the upper lid (fig 4 *f*)

ASSOCIATED MOVEMENTS IN OCULOMOTOR MUSCLES

Retraction of the upper lid on downward movement of the eyeball occurring after incomplete recovery of a third nerve palsy is often called the Fuchs' sign Fuchs [6] stated in 1917 that he was the first who,[7] in 1893 published such observations, and Coppez [8] agreed with him This is not correct, since Fuchs in his first paper cited the pertinent observation of Browning,[9] in 1890 It was actually Gowers [10] who, in 1879, described these phenomena for the first time His illustrations showed convincingly the abnormal retraction of the upper lid on downward movement of the eye, the so-called Fuchs sign

This phenomenon is often also called the Koppen sign or the Brixa-Koppen sign, in accordance with the publication of Koppen,[11] in 1894, and that of Brixa,[12] in 1897 The most popular designation is the pseudo-Graefe sign, coined by Koppen, since in the original Graefe sign, described for the first time in a case of exophthalmic goiter, the upper lid does not follow the downward movement of the eyeball It is interesting that Fuchs,[7] in his first publication, of 1893, remarked concerning the phenomenon observed in cases of oculomotor palsy that it reminded one

6 Fuchs, E Ueber die pathologische Mitbewegung der Lider, Jahrb f Psychiat u Neurol **38** 49, 1917

7 Fuchs, E Assoziation von Lidbewegung mit seitlichen Bewegungen des Auges, Beitr z Augenh, 1893, no 11, p 12

8 Coppez, H Sur le pseudo-signe de Graefe (signe de Fuchs), Arch d'opht **48** 385, 1931

9 Browning, F W Affections of the Muscular and Nervous Systems, Tr Ophth Soc U Kingdom **10** 187, 1890

10 Gowers, W R The Movements of the Eyelids, Med-Chir Tr **62** 429, 1879

11 Koppen, M Beitrage zur pathologischen Anatomie und zum klinischen Symptomencomplex multipler Gehirnerkrankungen, Arch f Psychiat **26** 99, 1894

12 Brixa Mitbewegung des Oberlides bei Bewegungen des Augapfels, Beitr z Augenh **26** 52, 1897

of the von Graefe symptom in exophthalmic goiter The name pseudo-Graefe sign is objectionable for several reasons It does not include the phenomenon of elevation of the eyelid on adduction and on elevation of the eyeball Furthermore, it does not include the phenomenon of dropping of the eyelid on abduction The name covers only the lifting of the eyelid on looking downward, whereas the most common and the most outstanding movement occurring after incomplete recovery from the third nerve palsy is the elevation of the lid on adduction of the eyeball There are cases, such as in this series, cases 2 and 3, in which the so-called pseudo-Graefe phenomenon is not shown, but all other phenomena usually associated with it are present Coppez [8] entitled his paper "the Pseudo-Sign of Graefe (Sign of Fuchs)" This double name can hardly contribute to simplification of the nomenclature

The phenomenon of involuntary lifting of the ptotic eyelid on passive closing of the normal eye was described in 1893 by de Mello Vianna [13] as *ptosis à bascule* and in 1896 by Paccetti [14] as *ptosi a bilancia* The latter name found entrance in textbooks (Purves-Stewart [15]) and in the literature (Alessandrini,[16] Caramazza [17]) In the discussion of this phenomenon, Gifford [18] spoke of "paradoxic elevation of the lid", Yanes,[19] of "paradoxic monocular ptosis" In their classic handbook on the neurology of the eye, Wilbrand and Sanger,[20] in describing this phenomenon, overlooked the intimate association of the adduction of the eye and the lifting of the eyelid, though their illustrations show this clearly They tried to explain this phenomenon as follows On exclusion of the normal eye, the full energy of the will is directed toward the frontal muscle of the affected side, a better contraction of which can thus be achieved However, the legend of one of their illustrations states that the patient was unable to lift the upper lid even when she tried "with the greatest exertion of will"

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13 de Mello Vianna, J Recherches cliniques sur les paralysies des muscles de l'œil, Thesis, Paris, no 417, 1893

14 Paccetti, G Sulle paralisi funzionali dei muscoli oculari, Policlinico (sez med) **3** 101, 1896

15 Purves-Stewart, J The Diagnosis of Nervous Diseases, ed 8, Baltimore, William Wood & Company, 1937, p 248

16 Alessandrini, A Contributo alla casistica della "ptosi a bilancia," Manicomio **38** 59, 1925

17 Caramazza, F Considerazioni cliniche su di un caso di ptosi a bilancia, Riv oto-neuro-oftal **7** 165, 1930

18 Gifford, S R Paradoxic Elevation of the Lid, Arch Ophth **22** 252 (Aug) 1939

19 Yanes, T R Paradoxic Monocular Ptosis, Arch Ophth **23** 1169 (June) 1940

20 Wilbrand, H, and Sanger, A Die Neurologie des Auges, Wiesbaden, J F Bergmann, 1900, vol 1, p 77

To speak of a "spasm" of the levator palpebrae muscle (Galezowski,[21] Bielschowsky[22]) or of "spastic contracture" (Wilbrand and Behr[23]) does not supply an accurate description, nor is it physiologically correct Spiegel and Sommer[24] described the pseudo-Graefe phenomenon thus "The paresis of the levator can be transformed in a contracture of this muscle" Other authors speak of "paradoxic movements"

To do physiologic justice to the phenomena that occur after incomplete recovery of a third nerve palsy, it is best to give them the only adequate and physiologically correct name—associated movements It is, physiologically speaking, an associated movement when the voluntary innervation of the rectus inferior causes a simultaneous, involuntary, automatic, unsuppressible—an associated—innervation of the levator palpebrae superioris

ASSOCIATED MOVEMENTS IN FACIAL MUSCLES

Observing these associated movements which occur after incomplete recovery from a third nerve palsy, one is struck by the similarity between these movements and those occurring after incomplete recovery from a facial nerve palsy Here, too, one sees typical associated movements, for instance, when a patient bares his teeth, he at the same time closes the eye on the affected side The postparalytic motor phenomena seen with palsies of the third and of the seventh nerve show many other points of similarity, which will be discussed later For the time being, suffice it to say that their associated movements seem to be of the same character

The pathophysiology of the associated movements so commonly observed in the chronic stage of facial palsy had been much discussed in the older literature but long remained controversial Lamy,[25] in 1905, in a short note, described the contractions following peripheral facial palsy and called them, as did Babinski,[26] *synérgiques paradoxales* Lamy

21 Galezowski, J Paralysie du moteur oculaire commun avec retraction du releveur de la paupiere, Rev neurol **19** 544, 1910

22 Bielschowsky, A Stellungsanomalien und Beweglichkeitsstorungen der Augen, Leipzig, Georg Thieme, 1922, p 37

23 Wilbrand, H, and Behr, C Die Neurologie des Auges in ihrem heutigen Stande, zugleich ein Erganzungsband zur Neurologie des Auges von Wilbrand und Sanger, Munich, J F Bergmann, 1927, pt 1, p 32

24 Spiegel, E A, and Sommer, I Ophthalmo- und Oto-Neurologie, Berlin, Julius Springer, 1931, p 154

25 Lamy, H Note sur les contractions "synergiques paradoxales" observées a la suite de la paralysie faciale peripherique, Nouv iconog de la Salpêtriere **18** 424, 1905

26 Babinski, J Hemispasme facial peripherique, Nouv iconog de la Salpetriere **18** 419 1905

attributed them to a misdirection of regenerating fibers, to a *restauration vicieuse* He compared these postparalytic movements of the facial muscles to movements occurring after surgical anastomosis of the accessory and the facial nerve This note of Lamy's remained unnoticed until Lipschitz,[27] in 1906, in a monographic discussion of the subject, advanced the same hypothesis He, too, assumed a misdirection of regenerating fibers, which grow indiscriminately from the central part of the injured nerve into the peripheral part, crossing and recrossing each other's pathways, mutually intruding into each other's channels This hypothesis was quickly accepted everywhere In the United States, Waterman,[28] in 1908, and Spiller,[29] in 1919, confirmed Lipschitz's view On the basis of this theory, Spiller tried to explain not only the associated movements but the contractures which occur in cases of partial recovery from facial paralysis The great authority of Spiller contributed much toward the popularity of Lipschitz's hypothesis It derived strong support from the studies of Ramón y Cajal[30] and Boeke[31] The former, in his classic work, said with regard to the restoration of the innervation in sectioned nerves

> the great majority, if not all, of the sheaths, instead of receiving the outgrowth of some axon which was present in them before the operation, are invaded by sprouts that have come from axons in other regions of the central stump

Boeke showed that regenerating fibers grow out distorted and without pattern and frequently branch at random Foerster[32] found that "much, undoubtedly, speaks in favor of the explanation of Lipschitz" To Cohn,[33] the great authority on peripheral nerves, this explanation seemed to be more correct than the older ones In recent years this subject has again been taken up by several authors They show a remarkable unanimity in their agreement with Lipschitz's view (Walsh and Craig[34],

27 Lipschitz, R Beitrage zur Lehre von der Facialislahmung nebst Bemerkungen zur Frage der Nervenregeneration, Monatschr f Psychiat u Neurol (supp) **20** 84, 1906

28 Waterman, G A Facial Paralysis A Study of Three Hundred and Thirty-Five Cases, Tr Am Neurol A **34** 63, 1908

29 Spiller, W G Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves, Arch Neurol & Psychiat **1** 564 (May) 1919

30 Ramón y Cajal, S Degeneration and Regeneration of the Nervous System, translated and edited by R M May, London, Oxford University Press, 1928, vol 1, p 276

31 Boeke, J De- und Regeneration des peripheren Nervensystems, Deutsche Ztschr f Nervenh **115** 160, 1930

32 Foerster, O, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1937, vol 3, p 600

33 Cohn, T, in Kraus, F, and Brugsch, T Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1924, vol 10, pt 1, p 224

Ehni [35], Coleman [36], Martin [37], Lyle [38], Howe, Tower and Duel [39]) It is remarkable that this hypothesis is the only one on this subject cited in leading textbooks and handbooks (Oppenheim,[40] Sahli,[41] Wexberg,[42] Monrad-Krohn,[43] Bing and Haymaker [44])

I myself accepted unreservedly Lipschitz's hypothesis, which has a tremendous appeal through its simplicity, as something self evident and indisputable The positiveness of the statements of the adherents of this hypothesis and its nearly universal acceptance were most impressive It seemed to explain not only associated movements but all other pathologic phenomena occurring after incomplete recovery from facial palsy as well

Nevertheless, scattered remarks are found in the literature which cast doubt on the omnivalidity of this hypothesis Holmes,[45] in 1928, expressed the belief that the cause of secondary contractures and of spontaneous twitchings of the facial muscles "is not definitely determined" Kramer [4] stated in 1936 that the interpretation of the contractures and associated movements after facial palsy still remains confused and that a satisfactory explanation of this phenomenon is still lacking The reviews given on this subject by Petz,[46] in 1933, and by Nussbaum,[47] in 1936, are confusing and inconclusive The latter stated

The great number of the theories and hypotheses reviewed here shows that it is difficult even today to gain a clearcut and all-embracing picture of the genesis and physiopathology of the late symptoms of peripheral facial palsy

34 Walsh, M N, and Craig, W M Posttraumatic Faulty Regeneration of the Vagus Nerve and Branches of the Cervical Plexus, Proc Staff Meet, Mayo Clin **15** 117, 1940

35 Ehni, G Facial Twitching, Proc Staff Meet, Mayo Clin **19** 129, 1944

36 Coleman, C C Surgical Lesions of the Facial Nerve with Comments on Its Anatomy, Ann Surg **119** 641, 1944

37 Martin, R C Repair of Peripheral Injuries of the Facial Nerve, J Nerv & Ment Dis **99** 755, 1944

38 Lyle, D J Neuro-Ophthalmology, Springfield, Ill, Charles C Thomas, Publisher, 1945, p 92

39 Howe, H A, Tower, S S, and Duel, A B Facial Tic in Relation to Injury of the Facial Nerve, Arch Neurol & Psychiat **38** 1190 (Dec) 1937

40 Oppenheim,[5] p 766

41 Sahli, H Lehrbuch der klinischen Untersuchungsmethoden, ed 6, Leipzig, Franz Deuticke, 1920, vol 2, p 935

42 Wexberg, E, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 9, p 118

43 Monrad-Krohn, G H Clinical Examination of the Nervous System, ed 7, New York, Paul B Hoeber, Inc, 1938, p 51

44 Bing, R, and Haymaker, W Textbook of Nervous Diseases, St Louis, C V Mosby Company, 1939, p 82

45 Holmes, G, in Osler, W Modern Medicine, ed 3, London, Henry Kimpton, 1928, vol 6, p 420

(Footnotes continued on next page)

HYPOTHESIS OF MISDIRECTED FIBERS FOR THE EXPLANATION OF ASSOCIATED MOVEMENTS IN OCULOMOTOR MUSCLES

The famous ophthalmologist Bielschowsky,[48] who died in 1940, and who in his time was the greatest authority on the motility of the eye, applied in numerous publications, the first appearing in 1910, the hypothesis of Lipschitz to explain associated movements after oculomotor palsy The leading French neurologist Thomas[49] stated in 1910, independently of Bielschowsky, that the associated movements of the oculomotor muscles after third nerve palsy could be explained in the same way as associated movements after facial nerve palsy—*par une régénération défectueuse des fibres nerveuses* Authors of various countries accepted readily the hypothesis of Lipschitz and Bielschowsky—Tamamscheff[50] (Russia), Coppez[8] (Belgium) and Abramowicz[51] (Poland), to name only a few In 1935 Bielschowsky[52] explained the pseudo-Graefe sign as follows

> Suppose that the continuity of the third nerve is interrupted by a trauma or a tumor In the course of healing, some of the nerve fibers which proceed from the central part of the trunk of the third nerve do not find their original sheaths in the peripheral part of the nerve but go astray, so that they arrive at muscles to which they do not belong For instance, the fibers from the nucleus intended for the internal rectus arrive not at this muscle but at the levator of the upper lid, so that the impulse for adduction produces lifting of the upper lid, even if it cannot be lifted by a direct innervation effort because the fibers coming from the levator nucleus have gone astray

In a review of this subject, Bielschowsky[53] stated in 1936 that the explanation given by Lipschitz for associated movements in the course

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46 Petz, M Ueber Kontrakturen und Mitbewegungen nach alter peripherer Facialislahmung, Arch f Psychiat **100** 379, 1933

47 Nussbaum, M Ueber die Physiopathologie der Spatsymptome nach Lahmungen im Gebiet des peripheren Teils des Nervus facialis, Inaug Dissert, Basel, 1936

48 Bielschowsky, A (*a*) Mitbewegungsphanomene bei Augenmuskellahmungen, Berl klin Wchnschr **27** 367, 1910, (*b*) Die Bedeutung der Bewegungsstorungen der Augen fur die Lokalisierung zerebraler Krankheitsherde, Ergebn d Chir u Orthop **9** 123, 1916, (*c*) Die Motilitatsstorungen der Augen, in Graefe, A, and Saemisch, T Handbuch der gesamten Augenheilkunde, ed 2, Berlin, Julius Springer, 1910, vol 8, pt 2, chap 11, p 395

49 Thomas, A, in discussion on Galezowski[21]

50 Tamamscheff, C Paradoxe Bewegungen des oberen Lides bei der Okulomotoriuslahmung (Pseudo-Graefesches Phanomen), Klin Monatsbl f Augenh **48** 479, 1910

51 Abramowicz, I On the Clinical Features of Oculomotor Paralysis, Klin oczna **11** 444, 1933, abstracted, Zentralbl f d ges Neurol u Psychiat **72** 244, 1934

52 Bielschowsky, A Lectures on Motor Anomalies of the Eyes, Arch Ophth **13** 33 (Jan) 1935

of facial palsy is the most plausible and the most natural one for the motor phenomena occurring after oculomotor nerve palsy In their monumental handbook on the neurology of the eye, Wilbrand and Behr,[54] leading German ophthalmologists, stated explicitly that they agree with the explanation of the pseudo-Graefe phenomenon as given by Bielschowsky,[48] which is based on the theory of Lipschitz

Extensive research has been done in recent years on the problem of associated movements in the muscles innervated by the oculomotor nerve Researchers and reviewers agree that these associated movements are due to "faulty peripheral nerve regeneration" (Bender[55], Bender and Alpert[56], Bender and Fulton[57], Ford and Woodhall[58], Ford, Walsh and King[59], Walsh and King[60], Walsh[61], Spiegel and Sommer[62], Dandy[63]) In his monumental work on ocular neurology, the only one of its kind in Spanish, Adrogué[64] accepted Bielschowsky's theory of the pseudo-Graefe phenomenon and cited the experimental work of Bender and Fulton as a confirmation of that theory In a book published in 1944, Ford[65] stated that the abnormal motor phenomena associ-

53 Bielschowsky, A Symptomatologie der Storungen im Augenbewegungsapparat, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 4, p 205

54 Wilbrand and Behr,[23] p 38

55 Bender, M The Nerve Supply to the Orbicularis Muscle and the Physiology of Movements of the Upper Eyelid, Arch Ophth **15**:21 (Jan) 1936

56 Bender, M B, and Alpert, S Abnormal Ocular and Pupillary Movements Following Oculomotor Paralysis, Arch Ophth **18** 411 (Sept) 1937

57 Bender, M B, and Fulton, J F Functional Recovery in Ocular Muscles of a Chimpanzee After Section of Oculomotor Nerve, J Neurophysiol **1** 144, 1938, Factors in Functional Recovery Following Section of the Oculomotor Nerve in Monkeys, J Neurol & Psychiat **2**·285, 1939

58 Ford, F, and Woodhall, B Phenomena Due to Misdirection of Regenerating Fibers of Cranial, Spinal and Autonomic Nerves, Arch Surg **36** 480 (March) 1938

59 Ford, F R, Walsh, F B, and King, A B Clinical Observations on the Pupillary Phenomena, Bull Johns Hopkins Hosp **68** 309, 1941

60 Walsh, F B, and King, A B Ocular Signs of Intracranial Saccular Aneurysms, Arch Ophth **27**·1 (Jan) 1942

61 Walsh, F B Certain Abnormalities of Ocular Movements Their Importance in General and Neurologic Diagnosis, Bull New York Acad Med **19** 253, 1943

62 Spiegel, E A, and Sommer, I Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc, 1944, pp 202 and 375

63 Dandy, W E Intracranial Arterial Aneurysms, Ithaca, N Y, Comstock Publishing Company, Inc, 1944, p 11

64 Adrogue, E Neurologia ocular, Buenos Aires, El Ateneo, 1942, p 128

65 Ford, F R Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed 2, Springfield, Ill, Charles C Thomas, Publisher, 1944, pp 69 and 70

ated with regenerated third and seventh nerves are "due to the misdirection of regenerating nerve fibers" Walsh[61] stated that it has been proved to be so

CRITIQUE OF THE HYPOTHESIS OF MISDIRECTION OF REGENERATING NERVE FIBERS

Despite these positive statements from authoritative neurologic, ophthalmologic and physiologic sources, the problem seems as yet unsolved To the hypothesis of misdirection of regenerating fibers, so widely accepted, the following objections must be brought forth

1 When one approaches the problem from a purely clinicophysiologic standpoint, it seems that such a lawless sprouting out of regenerating fibers, deviating from their course, must be considered the exception, not the rule It can hardly be assumed that all fibers go astray Of course it is not known how many misdirected fibers are necessary or sufficient to produce associated movements, but the universality of associated movements in a given case would imply a misdirection of all the fibers Even if and when a misdirection of regenerating fibers takes place, there is no proof that this misdirection is the cause of the ensuing manifold, widespread and intensive associated movements The direct deduction that anatomic changes produce such a physiologic effect cannot, and should not, be blindly accepted as the basis for discussion Also, if the regenerating fibers have the alleged strong and universal tendency toward misdirection which accounts for postparalytic associated movements, such movements should, then, always occur in every case of injury to the third or the seventh nerve, this is not the case Associated movements occur often after injury to the third or the seventh nerve, but by no means always

2 It would be understandable if misdirection of regenerating fibers were to occur only in cases of traumatic or surgical palsy, especially in cases in which nerves are sutured Here the nerve undergoes some displacement But one usually finds associated movements also in cases of simple "rheumatic" facial palsy and of infections of the third nerve, in which no mechanical trauma to the nerve could have taken place Associated movements appear, for instance, after facial neuritis in the fallopian canal, where the nerve is well protected against spatial changes Conspicuous associated movements occur in cases in which the nerve was not severed, in which the relationship of the central and the peripheral end of the nerve was not disturbed Here, regeneration in the old established paths could easily have taken place It is incomprehensible why such a misdirection, leading to intensive and extensive associated movements, should occur here at all

3 If misdirection of regenerating fibers of any import does take place on recovery of the nerve, it would be natural to assume that this

misdirection would be more intensive and extensive in surgical cases than in cases of primary neuritis or perineuritis Special investigations on this point are lacking From a review of the cases in the literature, however, together with the cases presented here, no support can be found for the assumption that traumatic or surgical palsies of the third or seventh nerve are more likely to be followed by associated movements than are purely neuritic ones I have often seen very marked associated movements after mild "rheumatic" facial palsy In cases of traumatic palsy there does not seem to be a greater tendency toward associated movements The following statement of Martin,[37] who has had wide experience along these lines, is remarkable in this connection

> Patients who have recovered from a Bell's palsy frequently have the corner of the mouth twitch when reflex winking occurs Post-traumatic cases do not show this often

This observation speaks positively against the hypothesis of misdirection, since according to it just the opposite should be expected—in the cases of post-traumatic palsy associated movements should occur more frequently

4 Postparalytic associated movements usually do not occur after infectious or traumatic lesions of nerves other than the third and the seventh Such a case has never come to my attention, either during or after World War I If associated movements were to occur in cases of palsy of spinal peripheral nerves after trauma, neuritis or operation, as they do in cases of third or seventh nerve palsy, the prognosis in such cases would indeed be quite different than it actually is Suppose these associated mass movements were to occur in cases of radial palsy The patient would move simultaneously all the radial muscles on innervating a single one! In such a case a limb would hardly be of practical use The mass movements would be almost unendurable, and surgical treatment of peripheral nerves would be almost nonexistent Occasionally associated movements have been seen with lesions of peripheral nerves But this has been reported only after use of sutures (Foerster,[32] Ford and Woodhall [58]), and even then these phenomena are rare

5 When an irregular sprouting of the fibers growing from the central into the peripheral end of a locally damaged nerve does occur, it is quite natural to assume that fibers from neighboring compartments would intermingle more readily If there are, e g, five parallel compartments, then compartments 1 and 2, 2 and 3, etc, would show more intermingling, and thus more mutual associated movements, than, for instance, compartments 1 and 5 A great amount of work has been done on morphologic segmentation and functional localization of the components of the oculomotor nucleus Reference may be made here

to the work of Brouwer [66] Riley [67] wrote an excellent review on this subject The latest investigation is that of Bender and Weinstein,[68] who concluded

> The functional representation of the ocular muscles in the oculomotor nucleus is as follows in dorso-ventral and rostro-caudal directions (1) sphincter pupillae (usually bilateral responses), (2) inferior rectus, (3) inferior oblique (?), (4) internal rectus, (5) superior rectus, and (6) levator palpebrarum The functional arrangement in the oculomotor roots is the same as in the nucleus

The textbooks accepted this scheme of the topography of the oculomotor nucleus, which is practically the same as that of Bernheimer,[69] published in 1897 On careful analysis of the associated movements in my cases, one would have to conclude (*a*) that fibers from neighboring compartments usually do not intermingle, (*b*) that fibers from remote compartments do intermingle most and (*c*) that the associated movements among them constitute the leading symptom in the postparalytic associated movements The nucleus and the fibers of the rectus superior lie next to those of the levator palpebrae One would expect that the fibers of these two muscles would intermingle most freely This, however, is not the case, and there are no associated movements from the levator palpebrae There are, to be true, associated movements from the rectus superior to the levator, but these are by no means prominent Fuchs [6] listed the elevation of the lid on looking upward as a "rare complication" Bielschowsky [48n] reported a case in which there were marked associated movements in the muscles supplied by the third nerve but no elevation of the lid on looking up The most important associated movements occur between the rectus internus and the levator palpebrae—and the nerve fibers of these two muscles are widely separated in their course! The pseudo-Graefe sign, which is so prominent in these associated movements, is due to a connection between the fibers to the rectus inferior and those to the levator palpebrae The compartments for these two muscles lie at the two ends of the elongated oculomotor nucleus and are separated by the compartments of the rectus superior, the rectus internus and the obliquus inferior ! To explain the pseudo-Graefe sign through misdirection of fibers, it must be assumed that the fibers from the rectus inferior have passed nearly all other fibers of the oculomotor nerve in order to reach the

66 Brouwer, B Klinisch-anatomische Untersuchung uber den Oculomotoriuskern, Ztschr f d ges Neurol u Psychiat **40** 152, 1918

67 Riley, H A The Central Nervous System Control of the Ocular Movements and Disturbances of This Mechanism, Arch Ophth **4** 640 (Nov) 1930

68 Bender, M B , and Weinstein, E A The Functional Pattern Within the Oculomotor Nucleus, Tr Am Neurol A **68** 48, 1942

69 Bernheimer, S Experimentelle Studien zur Kenntniss der Innervation der inneren und ausseren von Oculomotorius versorgten Muskeln des Auges, Arch f Ophth **44** 481, 1897

levator muscles, which are the most remote There can hardly be any explanation for such an elaborate misdirection

6 The cardinal feature in postparalytic associated movements of the third nerve is the ease with which the levator palpebrae reacts to impulses sent to other muscles This occurs also in cases in which the levator palpebrae is completely paralyzed Sattler,[70] explaining the pseudo-Graefe symptom, stated that here an impulse of innervation irradiates into pathways which are less damaged This is not quite correct, since the pathways—for instance, those for the levator palpebrae—may be completely blocked for voluntary innervation and still the pseudo-Graefe phenomenon may occur There is no doubt that the levator palpebrae may move on innervation of the rectus inferior or the rectus internus and otherwise be completely paralyzed Bielschowsky [22] reported such a case Here the paralyzed upper lid could not be lifted in the slightest, not even with the strongest effort The complete paralysis of the levator palpebrae means that none of the fibers from its nucleus has reached the muscle They must be totally misdirected to other muscles But where to? There is no evidence for such misdirection, since there are in cases of paralysis of the levator no associated movements in any other oculomotor muscle—not even in traces—when the levator is innervated It must, then, be assumed that all the fibers leading to the levator palpebrae have reached nowhere—that they have been blocked completely, a condition which is difficult to conceive This is all the more difficult when it is recalled that there are cases in which, in the presence of associated movements in the oculomotor muscles, there is complete paralysis of the levator palpebrae and of the rectus superior muscle—and no associated movement from these to other muscles! Adherents of the Lipschitz-Bielschowsky hypothesis owe an explanation as to how it is possible that some fibers get completely lost and why this happens predominantly to nerve fibers destined for the levator palpebrae

7 Associated movements in oculomotor muscles, with their cardinal symptom of automatic elevation of the lid on looking inward and downward, do occur in cases in which the levator palpebrae has recovered completely The literature is replete with such interesting reports Bielschowsky [52] described such a case in detail According to the text and judging from the illustrations, the levator palpebrae was completely normal On another occasion he spoke of a pseudo-Graefe phenomenon occurring when the ptosis had almost, or completely disappeared [48b]

70 Sattler, H Basedow'sche Krankheit, in Graefe, A, and Saemisch, T Handbuch der gesamten Augenheilkunde, Leipzig Wilhelm Engelmann, 1908, vol 9, pt 2 chap 14 p 79

Sinclair,[71] in classifying the numerous types of abnormal associated movements of the lids, listed group 4, in which there is no ptosis Hinkel[72] reported that in his case the ptosis disappeared Bender[7] based his first study of postparalytic movements of the third nerve on a case in which there was no ptosis Fuchs[6] stated " it can happen that the ptosis disappears and yet the pseudo-Graefe continues " If the levator palpebrae in the course of regeneration of the nerve after palsy has been restored to normal, it can mean only that all the fibers which belong to the levator palpebrae have reached their destination Its compartment is filled The *status quo ante* has been restored But in such a case associated movements may still be present spreading, say, from the rectus internus to the levator palpebrae How could this be possible if the levator palpebrae has become normal? Its complete restoration can mean only that the whole of its compartment has been filled, and with its own fibers, which are now in their respective places How, then, could, and why should, fibers of the rectus internus "squeeze" into the already completely filled compartment, and if some fibers of the rectus internus did penetrate the compartment of the levator, and fill it, together with the first arrived levator fibers, how, then is it possible that the other levator fibers could "squeeze" into this already filled compartment? The compartment of the levator must have been filled with its own fibers, since the muscle does not show the slightest sign of paresis A mass immigration into the compartment of the levator of the fibers innervating the rectus internus muscle would have to take place to explain the strong associated movement A few misdirected fibers could hardly account for such a powerful contraction of the levator palpebrae on innervation of the rectus internus In order to explain the phenomena of associated movements involving the levator muscle in the absence of ptosis, it must be assumed that one compartment can be filled beyond normal capacity at the expense of some other compartment This is difficult to conceive

8 The regenerating fibers growing from the point of lesion toward the periphery need time to reach their own, or other muscles, It is generally assumed that the axons grow at the rate of 1 mm a day If associated movements are due to misdirection, they should appear earlier with more distally located lesions of the third or the seventh nerve than with the more proximally located lesions From a cursory survey this does not seem to be the case Exact investigations on this subject, however, are lacking Case 2 raises another question Here, after a lesion of the oculomotor nerve which followed trauma to the skull,

71 Sinclair, W W Abnormal Associated Movements of the Eyelids, Ophth Rev **14** 307, 1895

72 Hinkel Das Pseudo-Graefe'sche Symptom in Anschluss an Augenmuskellahmungen, Inaug Dissert, Rostock, 1902

associated movements were noted thirty-five days after the injury How much earlier they might have appeared cannot be stated Dr J B de C M Saunders (personal communication) estimates the length of the oculomotor nerve from its emergence at the base of the brain to its insertion into the muscles as being 5 to 5 5 cm If the lesion occurred in the most proximal part of the nerve—which is most likely—the time interval would have been too short for the nerve to traverse this distance, especially if the growth of its fibers was complicated by aberration I have seen associated movements appear so early after infectious neuritis of the seventh nerve that the growing out of the damaged fibers into the muscles could hardly have taken place in so short a time The time element deserves special consideration in future discussions of this problem

9 It is difficult to establish clinically the diagnosis of a peripheral versus a nuclear third nerve palsy It is, however, a well known fact that nuclear palsies of the cranial nerves in general, and those of the third nerve in particular, do occur after injury to the skull From Tietze's [73] review of the literature one learns of the certain existence of such nuclear post-traumatic third nerve palsies Spiller [74] showed an isolated nuclear third nerve palsy histologically This was due to thrombotic closure of the small arteries supplying the nuclei of the oculomotor nerve As to the probable central origin of oculomotor nerve palsy which later leads to associated movements of the oculomotor muscles, it is interesting to note that Gowers,[10a] who first described a case of this condition, assumed that the lesion was "probably central" Koppen,[11] in a histologic study of his case, found striking vascular changes in the area of the nucleus of the third nerve Fuchs [7] assumed that a primary lesion of the nucleus existed in 2 of his cases, as did Galezowski [21] Wilbrand and Behr [23] even stated that "the pseudo-Graefe phenomenon can occur with both peripheral and—as is more often the case—with central lesions" As to the associated movements occurring after nuclear lesions of the seventh nerve, there are so many pertinent and well substantiated reports that it is hardly necessary to cite any of them here From what is known on this subject, it must be assumed that such movements do occur when the lesion is located in the nucleus of the seventh nerve itself Such a lesion to the nucleus or to its efferent system is, of course, not complete, either quantitatively or qualitatively, some elements capable of regeneration must remain

73 Tietze, A, in von Bruns, P Neue deutsche Chirurgie, Stuttgart, F Enke, 1916, vol 18, pt 2, p 129

74 Spiller, W G Bilateral Oculomotorius Palsy from Softening in Each Oculomotorius Nucleus, Névraxe **14** 125, 1913

intact, or otherwise no regeneration and no restoration of movement of any kind could take place When postparalytic associated movements occur—as they certainly do—with nuclear lesions of the third or the seventh nerve, it is difficult to comprehend, first, how such a misdirection could take place at all, especially with inflammatory or degenerative disease, and, second, how it could produce exactly the same results as does a peripheral injury to the nerve itself It would be quite natural to assume that if the nucleus was damaged no misdirection could occur and the fibers might have the opportunity to leave the nucleus in their preformed channels The whole theory of misdirection evidently is applicable only to the cases of lesions of the nerve trunk, and not to cases of nuclear lesions

10 The hypothesis of misdirection of regenerating fibers has one absolute prerequisite, a *conditio sine qua non*, so to say The lesion must lie on the trunk of the third or the seventh nerve before it branches off to the various muscles which participate in the mutual associated movements But it is a fact that associated movements do occur after damage to a single peripheral branch of the third or the seventh nerve, and this at some distance from the point where it leaves the main trunk Bittorf [75] described such cases involving the seventh nerve He saw, for instance, associated movements consisting of wrinkling of the skin of the chin on closing the eye in a case of an old, mild injury to the distal part of the ramus mentalis Furthermore, he saw associated movements extending to the platysma muscle in cases of isolated injury of the facial branch to the mouth Kramer [4] stated

> After injury to single branches of the facial nerve, for instance, after lesions incurred in duels or with bullet wounds of the cheek, which is followed by isolated paresis of the muscles of the upper lip, associated movements occur It is remarkable that in cases of such injury the innervation of the orbicularis oculi muscle, which had not been damaged, brings about an associated movement of the upper lip

I have observed such cases, which were described by a pupil of mine (Petz [46]) Since this report other similar observations have left no doubt in my mind that associated movements do occur on injury of a peripheral branch of the facial nerve, movements involving muscles innervated by branches of the nerve which have not been injured in any way

With respect to the third nerve, similar observations are on record Hinkel [72] saw associated movements in the oculomotor muscles when the lesion to the oculomotor nerve had occurred in the orbit In this connection, a remarkable case was described by Halpern,[76] but all too briefly A young man shot himself in the right temple in an attempt at

75 Bittorf, A Ueber Mitbewegungen im Facialisgebiet, Deutsche Ztschr f Nervenh **121** 221, 1931

76 Halpern, L On the Pseudograefic Symptom, Harefuah **8** 111, 1934

suicide The bullet remained at the base of the brain on the right side The right eye showed isolated complete ptosis After three months the patient displayed the pseudo-Graefe symptom He was unable to lift the ptotic lid, but it moved involuntarily when he looked downward Here there was an associated movement in the levator palpebrae on innervation of the rectus inferior muscle, and this in a case in which only the branch of the oculomotor nerve leading to the levator palpebrae muscle was injured

In those cases in which associated movements appear in facial or oculomotor muscles when only a terminal branch of the nerve to these muscles has been damaged, the theory of misdirection must fail completely According to this hypothesis, one would have to assume here a retrograde regeneration of the affected terminal branch to the main track of the nerve and forward regeneration along unaffected branches—an impossible assumption!

11 Associated movements, though of mild degree, may occur both in muscles supplied by the seventh nerve and in muscles supplied by the third nerve in cases in which no injury and no palsy has ever taken place These movements, thus, can occur in otherwise completely normal nerves Kramer [4] stated "In rare cases the same associated movements can be seen without a facial palsy having previously occurred" I have seen many a case of associated movements in the facial muscles in completely normal intelligent persons who had never been aware of this anomaly I observed it also in cases of extrapyramidal diseases and in 1 case of amyotrophic lateral sclerosis There are certain persons who show, so to speak, some kind of motor infantilism in their facial muscles, consisting in lack of differentiation, i e, a tendency to perform mass movements instead of single ones In the area of the third nerve, too, associated movements were noticed when no paralysis of the ocular muscles was or ever had been present So many definite cases of this kind are reported in the literature that there can be no room for doubt. Here a misdirection of regenerating fibers cannot be incriminated in any way

12 Associated movements in oculomotor muscles can exist as a congenital anomaly One of the first cases described, that of Browning,[9] belongs to this group Fuchs [7] compared this condition with the syndrome of Marcus Gunn which in most cases represents a congenital anomaly Friedenwald,[77] compiling cases of associated movements of the eyelids, found 12 in which the condition was congenital Of recently described cases of the congenital pseudo-Graefe phenomenon that of

77 Friedenwald, H On Movements of the Eyelids Associated with Movements of the Jaws and with Lateral Movements of the Eyeballs, Bull Johns Hopkins Hosp 7 134, 1896

Volmer [78] may be mentioned Here this abnormality could be seen in 6 members of a family, covering four generations on the paternal side In some cases of the congenital type there is absence of any other pathologic sign, such as ptosis, there are associated movements only In cases in which the condition is congenital, and no injury to the nerve has ever taken place, the theory of misdirection of regenerating fibers, of course, fails completely to give a satisfactory physiologic explanation

13 There is a rare condition—congenital or acquired—called cyclic or rhythmic oculomotor nerve paralysis This is characterized by alternating automatic phases of spasm and relaxation affecting various branches of the more or less paralyzed oculomotor nerve Selinger [79] reported the appearance of the pseudo-Graefe sign in the spastic stage in such a case Hicks and Hosford [80] observed the same phenomenon during both the spastic and the relaxed phase Here misdirection of fibers could not have taken place and could not be blamed for the associated movements

14 It is worth while to note that associated movements—of the same type as those which occur after incomplete recovery from facial palsy—do occur in facial muscles which have never been paralyzed but which have been the site of another hyperkinesis, the so-called hemifacial spasm Here, both the associated movements and the spasm urgently require a common explanation, which the hypothesis of misdirection does not and cannot offer The following is an illustrative case

A 55 year old man had suffered for three years from tonic-clonic spasms of the muscles of the right side of the face There were no objective signs otherwise The muscles of the right side of the face were normal in the intervals between spasm There was no indication of any source of irritation A psychogenic origin could be excluded by the fact that some of the tonic-clonic spasmodic movements of the muscles were such that they could hardly be imitated voluntarily Figure 5 *a* shows the patient at rest Hardly any abnormality can be seen Figure 5 *b* shows associated movements in the muscles of the corner of the mouth on closing of the eyes These associated movements occurred only on firm closing, and not on light closing Figure 5 *c* shows associated movements in the orbicularis oculi on baring of the teeth These associated movements occurred only in the facial muscles There were no associated movements in any of the facial muscles when the muscles

78 Volmer, W Erbliche, abnorme Mitbewegung des Oberlides, Klin Monatsbl f Augenh **73** 135, 1924

79 Selinger, E Cyclic or Rhythmic Oculomotor Paralysis, Arch Ophth **4** 32 (July) 1930

80 Hicks, A M, and Hosford, G N Cyclic Paralysis of the Oculomotor Nerve, Arch. Ophth **17** 213 (Feb) 1937

of the trigeminal nerve, for instance, were innervated, e g , when the patient squeezed a tongue blade tightly between his teeth All the photographs were taken while the patient was completely at rest The associated movements shown here, produced in other facial muscles when only part of them is innervated, cannot be regarded as a spasmodic contraction provoked by the voluntary movements This is true for the following two reasons (1) the associated movements produced here artificially ceased at once when the voluntary movement stopped, (2) these associated movements were not accompanied, as in a spontaneous spasm, with hyperkinesis in such forms as fine twitchings and fibrillations

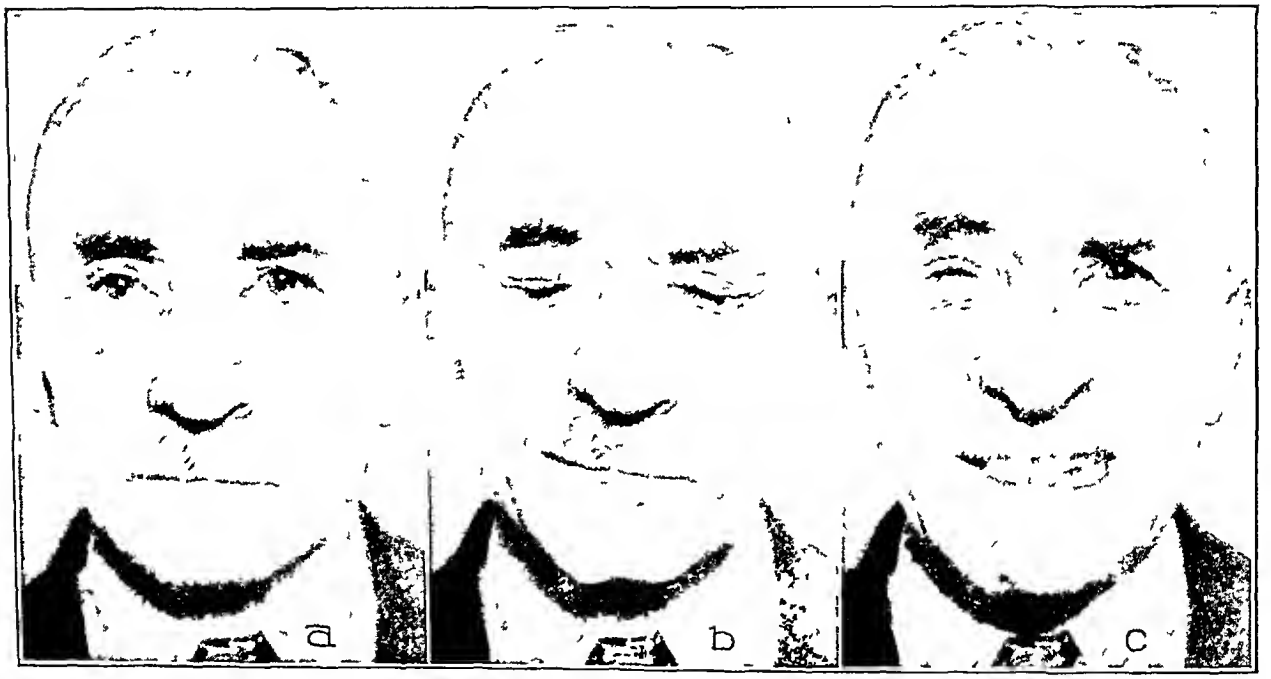

Fig 5 (case 5) —Associated movements in the facial muscles in a case of right-sided cryptogenic hemifacial spasm The patient is shown (*a*) at rest, (*b*) with his eyes closed and (*c*) showing his teeth

Since I have found associated movements in cases of cryptogenic hemifacial spasm, former patients with this condition have been reexamined for associated movements, and every new patient has been checked for this condition Associated movements have been found present in every case and were mostly unnoticed by the patients even when the condition had persisted for many years [80a]

This constant association of cryptogenic hemifacial spasm with associated movements in the affected muscles is a remarkable phenomenon which is of import to the present discussion Here, there are associ-

80a Pitres, A , and Abadie, J Hémispasmes syncinétiques de la face, Nouv iconog de la Salpêtriere **26** 363, 1913

ated movements of the facial muscles exactly as they are seen after paralysis, but certainly no misdirection of any fibers could account for their existence

15 If the misdirection of regenerating fibers were to produce associated movements, it would be quite justifiable to assume that—since such a misdirection is completely anarchistic, lawless, and cannot have any established pattern—the ensuing associated movements should be of a great variety The movements should vary in different persons and should range, so to speak, from 1 to 100 per cent in their variations and modifications This is not the case There is a definite pattern for the associated movements of the seventh nerve each muscle of the seventh nerve contracts simultaneously on voluntary innervation of any other facial muscle This is, of course, most conspicuous in the mutual reactions of the orbicularis oculi muscle and the muscles innervating the corner of the mouth But less prominent muscles, such as the platysma, participate also in the associated movements All the facial muscles act here as a unit These muscles contract not only on voluntary innervation of a single muscle but on reflexive contraction of any of them Many a reflex described in the regenerating facial muscles is nothing else than an associated movement Mondino [81] described in 1907 a "special reflex observed with facial contracture In cases of facial contracture occurring in association with peripheral nerve palsy, tapping the supraorbital nerve at the point of its emergence produces a reflexive contraction in the muscles of the lower branch of the facial nerve" Referring to Mondino, Purves-Stewart [82] stated "The spastic facial muscles can also be made to contract reflexly by tapping lightly over the point of emergence of the most accessible branch of the fifth, viz, the supraorbital nerve" Buzzard [83] reported the same phenomenon "A tap on the supra-orbital branch of the fifth nerve often produces a contraction of the muscles at the corner of the mouth in this condition" As was pointed out elsewhere (Wartenberg [84]), this tapping elicits the orbicularis oculi reflex, consisting of a contraction of this muscle This reflex has, of course, no connection with the supraorbital nerve, since tapping the glabella or any other point around the muscle can elicit it This reflexive contraction of the orbicularis oculi muscle produces, in turn, an associated contraction in the muscles innervated by the lower branch of the facial

81 Mondino, C Di uno speciale riflesso che si osserva nella contrattura facciale, Riv di pat nerv **12** 49, 1907

82 Purves-Stewart,[15] p 269

83 Buzzard, E F Varieties of Facial Spasm and Their Treatment, Practitioner **91** 745, 1913

84 Wartenberg, R Studies in Reflexes, Arch Neurol & Psychiat **51** 113 (Feb) 1944

nerve This "reflex" was rediscovered by Myerson [85] in 1920 In the description of this phenomenon, he was more correct than Mondino when he stated "Tapping the forehead or the bridge of the nose causes a contracture (reflex) of the affected corner of the mouth" The muscles of the chin and the platysma muscle also participate in these mutual movements, both on voluntary and on reflexive stimulation of other facial muscles I observed repeatedly that on tapping the glabella, as for the elicitation of the orbicularis oculi reflex, there was a distinct contraction of the platysma, on its medial border, under the chin ´ Rendu [86] stressed the fact that the superior and posterior auricularis muscles, innervated by the facial nerve, also participate in the associated movements There is an involuntary upward movement of the auricle on contraction of the orbicularis oculi muscle Ford and Woodhall,[58] in describing their case of "rheumatic" palsy of the seventh nerve, remarked

> On repeated tests it was evident that whenever the patient moved any part of the right side of the face every muscle supplied by the seventh nerve on that side contracted to some extent

Coleman [87] stated

> the entire facial musculature on the affected side is made a single functional unit and with every movement the facial muscles move *en masse*

All this serves to demonstrate the total character of the associated movements in the muscles controlled by the seventh nerve This is due to the fact that all the facial muscles participate in these movements on a mutual basis These movements are based on the "all for one" principle This pattern of associated movements is constant in all cases No muscle is excluded, no muscle, or combination of muscles seems to have any dominant priority, although, of course, the visible manifestations of these movements are more prominent in some muscles than in others Apparently, the function and location of these muscles make their movements more discernible Occasionally these movements are only rudimentary This is apparently due to a severe lesion of "the final common path" Such a lesion may block the path almost completely and permit only vestigial impulses to pass The associated movements of the facial nerve seem to prove that the underlying lesion has transformed all the facial muscles into a compact, inseparable unit, with all participants equally active If this is due to misdirection of regenerating fibers, one must

85 Myerson, A Reflex Phenomena in the Contracture Stage of Peripheral Facial Paralysis, J Nerv & Ment Dis **52** 239, 1920

86 Rendu, R Syncinésie palpebro-auriculaire dans la paralysie faciale, J de méd de Lyon **7**·417, 1926

87 Coleman, C C Results of Facioh ypoglossal Anastomosis in the Treatment of Facial Paralysis, Ann Surg **111** 958, 1940

assume that this misdirection occurs from all the compartments of the facial trunk and occurs with absolute regularity in every case, that the fibers from any one compartment go constantly astray to all other compartments and are equally distributed among them and that no compartment is spared Needless to say, such an assumption is not tenable

There is a definite pattern also for the associated movements of the muscles supplied by the third nerve, which consists of (1) ready responsiveness with which the levator palpebrae and the rectus internus muscle react to any innervation of any other muscles of the third nerve and (2) close association of movements between the rectus internus and, to a lesser degree, the rectus inferior on one side and the levator palpebrae on the other side

In the literature one finds numerous references to the stereotyped, monotonous associated movements in the muscles of the third nerve Sinclair's [71] classification of the abnormal associated movements of the eyelids has, in series 2, cases in which contraction of the levator palpebrae superioris automatically follows the contraction of the rectus internus This series may be regarded as a paradigm for all pathologic associated movements of the muscles of the third nerve These two muscles show the greatest tendency toward associated movements Ford, Walsh and King [59] stated correctly and very pertinently "No matter what movement is attempted, the bulb is adducted and the lid lifts" This regularity of associated movements is so striking that an attempt has been made to explain it by assuming that the regenerating fibers, in their deviation from their own course, prefer certain routes and that these particular routes are most commonly entered Bielschowsky [22] said, for instance, that "the route to the levator palpebrae appears to be especially easily accessible" No reasonable explanation can be given why certain regenerating fibers should prefer to enter certain routes which belong to other fibers and why these routes should be so easily accessible How is it possible to explain why the fibers which belong in the compartment of the rectus internus insist, with constant stubbornness, on going astray in one particular direction while "jaywalking," namely, into the compartment of the levator palpebrae, which is not even their neighboring compartment? Whatever may be the explanation for the pattern of the associated movements in the muscles of the seventh and third nerves, there is no doubt that such a pattern exists and that the associated movements do not display any chaos in their manifestations A misdirection of fibers, which in itself can be only completely irregular, could not produce such well behaved associated movements Observing them, one must say "There is too much order in this disorder!"

The associated movements after incomplete recovery from the seventh or the third nerve palsy are thus always the same, regardless of the site and nature of the disorder, its cause and the condition of the patient Associated movements appear in the facial muscles no matter whether the lesion is diffuse or localized or where in its course the nerve is affected I have seen exactly the same associated movements in the facial muscles after a local injury and after recovery from Guillain-Barré-Strohl polyneuritis As far back as 1872, Hitzig [88] mentioned that the associated movements seem to be completely independent of the site and the nature of the lesion The same view was held by Lipschitz,[27] according to whom only the severity of the lesion is important The same applies to the third nerve Von Michel,[89] in 1908, stressed that the site and the causes of the third nerve palsy seem to be irrelevant to the appearance of associated movements Coppez [8] and Camison [90] emphasized this recently The same associated movements in the oculomotor muscles have been observed after such diversified morbid conditions affecting the third nerve as pressure from a saccular aneurysm of the internal carotid artery, polioencephalitis superior acuta, trauma to the skull, syphilis-tabes-dementia paralytica, postdiphtheritic polyneuritis, arteriosclerosis, sinus empyema, echinococcus orbitae and basal meningitis It is hardly conceivable that the regenerating fibers would be misdirected in all these cases in exactly the same way and thus lead to exactly the same associated movements

This ever present pattern of the associated movements which occurs after any lesion to the third or the seventh nerve anywhere along its course demands that one look for the genesis of such movements in the place of origin of these nerves—their nuclear structure

16 Associated movements in the oculomotor or facial muscles, once established, remain for the duration of the patient's life It is hardly necessary to cite from the literature, as reports are unanimous on this matter, suffice it to mention the case of Gowers [91] in which associated movements "were still considerable" twenty-five years after the attack The second case in my series presents an unusual exception to the general rule that the associated movements in the

88 Hitzig, E Ueber die Auffassung einiger Anomalieen der Muskelinnervation, Arch f Psychiat **3** 312 and 601, 1872

89 von Michel, J Die Krankheiten der Augenlider, in Graefe, A, and Saemisch, T Handbuch der gesamten Augenheilkunde, ed 2, Leipzig, Wilhelm Engelmann, 1908, vol 5, pt 2, p 440

90 Camison, A Un caso de pseudo-signo de Graefe, Rev cubana de oto-neuro-oftal **2** 235, 1933

91 Gowers, W R A Manual of Diseases of the Nervous System, ed 2, Philadelphia, P Blakiston's Son & Co, 1907, vol 2, p 243

muscles innervated by the third nerve do not recover Here a spontaneous and complete recovery took place, and this without any therapy It must be assumed that, though extremely rare, the associated movements may regress completely, especially in cases of mild palsies, in some they do not appear at all However, I have never seen or heard or read of a patient who has recovered from, or shown the least improvement in, associated movements after a lesion of the seventh nerve The stubborn persistence of the postparalytic associated movements with palsies of the third and seventh nerves is in sharp contrast to the duration of the movements which follow anastomosis of the peripheral nerves Here the resulting pronounced associated movements can be improved with exercise and therapy With regard to hypoglossofacial and spinofacial anastomosis, Peet[92] stated "Reeducation of the cortical centers seems to take place, as in many patients the associated movements practically disappear" There is no such therapy for the associated movements of the facial or oculomotor muscles, they remain permanent

17 If and when after an injury to a nerve regenerating fibers go astray, this could, evidently, produce associated movements only in the area of the muscles supplied by this nerve However, many a feature of a seventh or a third nerve palsy seems to indicate that the lesion must have spread centrally, far beyond the peripheral nerve trunk and its nucleus Associated movements have been observed after a peripheral seventh nerve palsy which seem to indicate that the connection between this nerve and the fifth was involved Jolly[93] observed in a case of bilateral peripheral facial palsy the following peculiar associated movement Whereas the patient was completely unable to lift the corner of his mouth, he could perform this movement on the left side the moment he clenched his teeth tightly Here a contraction of the masseter muscle brought about an associated movement from the fifth to the seventh nerve Oppenheim[40] observed a palsy of the right side of the face in which a jerking of the lower jaw to the left occurred simultaneously with the blinking of the left eye This is an associated movement from the seventh to the fifth nerve Associated movements of the same kind were observed by Ornsteen[94] in a patient with acute polyneuritis and facial diplegia In this case each voluntary and involuntary movement of the eyelid

92 Peet, M M The Cranial Nerves, in Lewis, D Practice of Surgery, Hagerstown, Md, W F Prior Company, Inc, 1944, vol 12, chap 2, p 63

93 Jolly Ueber einen Fall von doppelseitiger Facialislahmung, Deutsche med Wchnschr **26** 173, 1900

94 Ornsteen, A M Palpebromandibular Synkinesis in a Patient with Acute Polyneuritis and Facial Diplegia, Arch Neurol & Psychiat **34** 625 (Sept) 1935

was synchronously associated with an involuntary short, sharp movement of the jaw Here, again, one is dealing with an associated movement from the facial to the fifth nerve in a case of peripheral facial nerve palsy The phenomenon was not reversible, i e, the movement of the mandible did not cause involuntary associated movement of the eyelid However, in the case of peripheral facial palsy described by Alajouanine and associates [95] the associated movements of the seventh and the fifth nerve were mutual and reversible Kramer [96] observed associated movements in the paretic facial muscles on innervation of the facial muscles on the normal side A case of a physiologically interesting congenital condition was reported and illustrated by Lyle [97] In a middle-aged woman the face and eyes were perfectly normal at rest, but when the patient retracted the corners of her mouth this voluntary movement caused the right eye to proptose and roll downward and slightly outward, and both lids to retract Lyle assumed that the fibers between the facial and the oculomotor nerve made a wrong "hook-up" Some "hook-up" must certainly have been at play, but it is hardly possible to assume that both nerves had intruded into each other's pathways in their peripheral course

After oculomotor palsy, too, associated movements which trespass on the area of this nerve can be observed Suffice it to mention the well known jaw-winking phenomenon of Marcus Gum Here, after a third nerve palsy with ptosis, we have associated movement from the fifth to the third nerve elevation of the upper lid on movement of the jaw This, by the way, is undoubtedly a phylogenetically archaic phenomenon, seen in fish physiologically A remarkable instance of associated movements with third nerve palsy was described by Ascher [98] Here the Marcus Gunn phenomenon appeared and disappeared in the course of syphilitic palsy of the third nerve A 44 year old patient with syphilis had complete palsy of the right third nerve After the palsy had existed for six months and the patient had received intensive antisyphilitic treatment, he noticed that the upper lid, previously unmovable, rose automatically on opening the mouth and on chewing After one week, this phenomenon dis-

95 Alajouanine, T , Thurel, R, and Albeaux-Fernet, M Paralysie faciale périphérique avec dissociation des activites volontaire et reflexe, Rev neurol **1** 398, 1934

96 Kramer,[4] p 351

97 Lyle,[38] p 91

98 Ascher, K Auftreten und Verschwinden des Marcus Gunnschen Kiefer-Lid-Phänomens während des Ruckgangs einer luischen Ptosis, Med Klin **33** 1259, 1937

appeared and the upper lid regained its voluntary motility, but other oculomotor muscles remained paralyzed Associated movements are further observed with third nerve palsy between muscles of this nerve and the facial muscles, for instance, the musculus frontalis Very common in cases of third nerve palsy are associated movements between the third and the sixth nerve This may occur with the sixth nerve also being involved or remaining intact Thus, the associated movement of raising the eyelid on abduction of the eye is not uncommonly observed This is wrongly called Friedenwald's sign It was described by Phillips [99] in 1887, whereas Friedenwald [100] described it in 1893

A physiologically significant observation along this line was briefly reported by Goodhart and Balser [101] In their case a man with sequelae of epidemic encephalitis showed the unusual phenomenon of inability to open the voluntarily closed eyes, in order to do so, he was obliged to carry out a movement of extreme hyperextension of the head Here, again, there is associated movement, namely, from the muscles which retract the head to the levator palpebrae This shows once more how easily and readily the movements of the levator palpebrae are linked with those of remote muscles

Needless to say, in all these instances in which associated movements appear with seventh or third nerve palsy which involve areas beyond the distribution of these nerves, it is impossible to incriminate misdirection of fibers The fibers of the third and the seventh nerve could not possibly grow by mistake into compartments of the fifth and the sixth nerves, or vice versa To explain these conditions, it must be assumed that the underlying cause acts centrally rather than on the trunk of the nerves, as set forth by the hypothesis of misdirection

Comment—After all that has just been said in criticism of the hypothesis of the misdirection of regenerating nerve fibers, it must be admitted that some of these seventeen points may be weak, some argumentation not quite convincing, some statements neither proved nor possible to prove at present However, taken as a whole, these points convey the definite impression that the hypothesis of misdirection of fibers as an explanation for associated movements in the muscles innervated by the third and seventh nerve is untenable, despite the fact that a galaxy of such names as Babinski, Andre Thomas, Bielschowsky and Fulton is behind it

99 Phillips, S Associated Movement of Upper Lid with Movement of Eyeball, Tr Ophth Soc U Kingdom **7** 306, 1887

100 Friedenwald, H Movements of the Upper Eyelid Associated with Lateral Movements of the Eyeball, Arch Ophth **22** 349, 1893

101 Goodhart, S P, and Balser, B H Neurological Cinematographic Atlas, New York, King's Crown Press, 1944, p 48

ASSOCIATED MOVEMENTS AFTER LESIONS OF THE THIRD OR THE SEVENTH NERVE AS COMPARED WITH THOSE AFTER LESIONS OF THE PYRAMIDAL TRACTS

Another approach to this problem is the comparison of associated movements occurring after injury to the third and seventh nerve with those which occur after lesions of the pyramidal tracts. Walshe[102] regarded the associated movements of hemiplegia as postural reactions, as variations in muscle tone attitude rather than as movements in the strict physiologic sense. They were, in his opinion, tonic or postural reflex reactions allied "to the tonic neck and labyrinthine reflexes of Magnus and de Kleijn." But the term "associated movements," so widely accepted (*Mitbewegungen* of the German, *mouvements associés* of the French), is more in keeping with the phenomena as they appear clinically. The associated movements in the territory of the cranial nerves can be defined in the same way as Riddoch and Buzzard[103] defined associated movements in hemiplegia:

> automatic activities which fix or alter the posture of a part or parts when some other portion of the body is brought into action either by voluntary effort or by artificial reflex stimulation

Whether occurring in the face or in the extremities, they must, clinically, be regarded as similar, and it is most interesting to note that as far back as 1896 Friedenwald[77] said of associated movements acquired with third nerve paralysis that they "belong in the same category as those associated movements observed in hemiplegia." This profound remark of Friedenwald's remained completely unnoticed.

There are various kinds of associated movements which occur with lesions of the pyramidal tract. They may be generalized, producing an exaggeration of the hemiplegia posture, or they may be symmetric, imitating on the paretic side the movements performed on the normal one. They may be coordinated and consist of synergic movements in muscles of an extremity other than in those directly innervated. The French called them *synciné sies de coordination*. There are numerous instances of such coordinated associated movements. Take, for instance, the so-called tibialis sign of Strumpell: On voluntary bending of the outstretched leg at the hip joint, a simultaneous involuntary and insuppressible dorsiflexion and supination of the homolateral foot ensues. This is an associated movement of the same kind which occurs with oculomotor palsy when the patient,

102 Walshe, F. M. R. On Certain Tonic or Postural Reflexes in Hemiplegia, with Special Reference to the So-Called "Associated Movements," Brain **46**:1, 1923.

103 Riddoch, G., and Buzzard, E. F. Reflex Movements and Postural Reactions in Quadriplegia and Hemiplegia, Brain **44** 397, 1921.

moving the paretic eye inward, simultaneously raises his paretic upper lid, a movement which occurs completely automatically and is not suppressible It is remarkable that many diagnostic signs of hemiplegia (often called reflexes) are based on associated movements To list a few Raimiste's abduction and adduction sign consists of involuntary abduction or adduction of the spastic leg on corresponding movement of the normal leg against resistance Babinski's trunk sign consists of flexion of the thigh on attempting to rise from the supine position, this is an associated movement of the flexors of the thigh on movement of the trunk muscles In Néri's leg sign, bending of the knee is associated with bending of the thigh Saethre's sign consists of abduction of the leg associated with flexion of the hip and knee joints Strumpell's pronation sign is a pronation of the forearm on bending of the elbow Wartenberg's thumb sign consists of an opposition, adduction and flexion of the thumb on bending the fingers against resistance Souques' phenomenon of the interosseus muscles consists of extension and abduction of the fingers on raising the arm All these signs are associated movements which, in my opinion, constitute the fundamental phenomenon of the pyramidal lesion

Both the associated movements in the extremities after a lesion of the pyramidal tract and the associated movements seen after lesions of the third and seventh nerves dominate the clinical picture They not only have a striking similarity at the first glance but reveal a close relationship on detailed examination In both instances the essential stimulus is a voluntary or an involuntary contraction of muscles Actual excursion of movement of the primary contracted muscle is not necessary, only a strong tonic muscular contraction is needed Some degree of hypertonus is an essential preliminary to the development of associated movements in both areas, some degree of hypertonus is distinctly seen also in the facial muscles In both conditions a movement which cannot be performed on voluntary stimulation of the muscle can be carried out as an associated movement on direct stimulation of other muscles In both conditions movements which appear as associated movements may exceed the normal response They are stereotyped, constant in their form, do not vary under the modes in which they may be produced and are resistant to therapy

SYMPTOMS OF LESIONS OF THE THIRD OR THE SEVENTH NERVE AS COMPARED WITH SYMPTOMS OF LESIONS OF THE PYRAMIDAL TRACT

In comparing the sequelae of a lesion of the pyramidal tract with those of a lesion of the third or seventh nerve, one may say that the two conditions are characterized by associated movements which are,

to say the least, similar These two conditions have—strange as it may seem at first glance—features in common in addition to these associated movements The features may be summarized as follows

1 There is weakness of the affected muscles

2 There is contracture of the muscles These contractures are self evident in the facial muscles They are present when associated movements are observed But muscular contractures occur, though seldom, also in cases of paralysis of the third nerve I mean, of course, not paralytic contractures of the unopposed muscles of the unaffected nerves but contractures of the oculomotor muscles proper Cohn and Isakowitz [104] showed that contractures may occur in the course of ophthalmoplegia in the paretic ocular muscles In their case of ophthalmoplegia due to syphilitic basilar meningitis there was a pronounced contracture of the levator palpebrae Coppez,[8] too, spoke of contracture in the affected oculomotor muscles and cited Behr The readiness with which the levator palpebrae reacts with contraction to many outside impulses and the occasionally abnormal range of this contraction speak for a latent state of spasticity

3 There are spontaneous hyperkinesias both in spastic extremities after a lesion of the pyramidal tract and in partially recovered paretic muscles innervated by the third or the seventh nerve With regard to the seventh nerve, it is of course extremely difficult to distinguish these spasmodic contractions from associated movements subsequent to the blinking of the eye But there is ample evidence that, besides these associated movements, there are postparalytic facial spasms, some of which are rhythmic Gowers,[105] having discussed the post-paralytic movements of the seventh nerve, stated that "in many cases another symptom is added after a time—spontaneous twitchings, isolated spasmodic contractions, recurring at irregular intervals, and affecting chiefly the zygomatici" Lipschitz, the father of the hypothesis of misdirection, began his monograph devoted to the postparalytic phenomena after seventh nerve palsy by saying that he was going to explain three points (1) associated movements, (2) spontaneous contractions which occur from time to time in the paralyzed area and (3) the exaggeration of reflexive irritability in the formerly paralyzed half of the face Ballance [106] claimed that the spontaneous contractions of the muscles of the face in man—when recovery from paralysis of the face is long delayed and more or less imperfect—are

104 Cohn, T, and Isakowitz Kontrakturen paretischer Augenmuskeln, Deutsche med Wchnschr **52** 1473, 1926

105 Gowers,[91] p 242

106 Ballance, C The Operative Treatment of Facial Palsy with Observations on the Prepared Nerve Graft and on Facial Spasm, J Laryng & Otol **49** 709, 1934

the common and permanent result of long-continued medical treatment It is not quite certain what he means here by "spontaneous contractions" In another work (Ballance and Duel[107]) the so-called spontaneous spasms are certainly considered as associated movements In any case, it is completely erroneous to assume that spasmodic contractions or associated movements after facial palsy have anything to do with treatment They are part and parcel of the postparalytic phenomena, and treatment neither produces them nor influences them essentially

Such spontaneous involuntary spasmodic contractions occur also in paralyzed muscles of the third nerve In one of the first papers on associated movements after oculomotor paralysis, Fuchs,[7] in 1893, described a case (case 3) in which rhythmic contractions of the levator occurred Von Bechterew[108] was one of the first to describe, in a case of third nerve palsy of syphilitic origin, a rhythmic spasm of the levator Of the recent publications on this subject, that of Bollack[109] may be mentioned The so-called cyclic oculomotor nerve paralysis, about which a voluminous ophthalmologic literature exists, probably belongs here In this condition there is a paralysis of the oculomotor nerve with alternating phases of clonic spasm and relaxation of its muscles Reference might be made here to Bielschowsky's[52] review of this subject He localized the lesion in the region of the nucleus of the third nerve A remarkable case of this kind, in which the oculomotor nerve palsy was congenital, was described by Kubik[110] In a case reported by Stein[111] the palsy was acquired early in life Some observers stress the automatic and rhythmic character of the movements Walsh and King[60] described 1 of their cases as follows

The patient, a man of 23, had exhibited what appeared to be complete oculomotor nerve paralysis on the left for fifteen years At irregular intervals the left lid surged open and remained elevated for a few seconds or for as long as several minutes The elevation might occur spontaneously or might be produced by bathing of the face in cold water The patient stated that elevation of the lid invariably appeared when he lost his temper or became interested in an attractive member of the opposite sex

107 Ballance, C, and Duel, A B The Operative Treatment of Facial Palsy, Arch Otolaryng **15** 1 (Jan) 1932

108 von Bechterew, W Ophthalmoplegie mit periodischer unwillkurlicher Hebung und Senkung des oberen Lides, paralytischer Ophthalmie, und einer eigenartigen optischen Illusion, Deutsche Ztschr f Nervenh **16** 209, 1900

109 Bollack, J Retraction spasmodique de la paupiere superieure consecutive a une paralysie de la troisieme paire, Rev d'oto-neuro-opht **13** 452, 1935

110 Kubik, J Ueber kongenitale Okulomotoriuslahmung mit erworbener zyklischer Innervation des inneren Okulomotoriusastes des Levator palp sup, Klin Monatsbl f Augenh **73** 131, 1924

111 Stein, R Okulomotoriuslahmung mit zyklischer Innervation der inneren Augenmuskeln, Med Klin **27** 350, 1931

With lesions of the pyramidal tract there are, too, such involuntary spasmodic contractions—for instance, in patients with transverse lesions of the spinal cord A rhythmic flexor withdrawal reflex, or a rhythmic Babinski toe sign, and alternating flexion and relaxation of the spastic extremities are observed These occur with slight or with extensive movement of the extremities Walshe [112] stated that involuntary flexor spasms occurring in cases of paraplegia in flexion are "characterized by complete intermissions of the spasm, which result in the production of alternating flexion and extension movements"

The spasmodic contractions in the paretic facial or oculomotor muscles may be considered, to say the least, as an analogue of the spasmodic contractions occurring in spastic extremities In both instances they occur either on peripheral stimulation or without it, or perhaps on some stimulation the nature of which cannot be determined In both instances these spasmodic contractions may be rhythmic, but they are always completely involuntary

4 In both conditions there are certain definite patterns for the associated movements, as well as for the spasmodic contractions They always recur in a stereotyped manner

5 There is hyperreflexia in both conditions Strumpell [113] emphasized the exaggerated reflexive irritability after facial nerve palsy, as did Hitzig [88]

6 In both conditions the associated movements, the contractures, the spasmodic contractions and the increased reflexive activity are permanent and not amenable to treatment

7 The associated movements can appear on the basis of a congenital defect and are not directly dependent on the degree of palsy

8 The hyperkinetic manifestations are independent both of the nature and of the location of the lesion

9 In both conditions there is an incubation period between the occurrence of the lesion and the appearance of the hyperkinetic phenomena

10 The motility shows a phylogenetic regression in both conditions. Primitive mass movements are brought to light, and phylogenetically older muscles come into play The highest, and later acquired, functions are particularly disturbed, especially those of greater complexity and greater differentiation A dedifferentiation takes place This is self evident in a lesion of the pyramidal tract, but the same is true also for facial nerve palsy It is a well established fact that the facial muscles

112 Walshe, F M R The Physiological Significance of the Reflex Phenomena in Spastic Paralysis of the Lower Limbs, Brain **37** 269, 1914

113 Strumpell, cited by Oppenheim,[5] p 735

started phylogenetically as a single unit but have undergone a differentiation in the course of development In facial palsy the associated movements show a phylogenetic regression, exactly as with a lesion of the pyramidal tract, the facial muscles have lost their ability to contract individually, a mass movement appears instead

As to the muscles innervated by the third nerve, it may be assumed that the great tendency of the levator palpebrae and of the rectus internus toward associated movements has some phylogenetic significance They are teleologically the most important muscles for the act of gazing, since the prerequisite for any visual act and for fixating a near object is opening of the eye and inward movement of the eyeball These phylogenetically older movements are preserved and are ready to spring into action on any stimulus These movements constitute what could be called the "fixation reflex," in analogy to the "flexor withdrawal reflex"

Thus, in the light of this confrontation, phylogenetically old movements come to the fore, both with lesions of the pyramidal tract and with those of the seventh or third nerve According to this view, the levator palpebrae and the rectus internus show increased reflexive activity with a third nerve palsy, exactly as the flexors of the lower extremities do with transverse lesions of the spinal cord

Walsh and King [60] and Ford and Woodhall [58] gave different explanations of the striking fact that the levator palpebrae and the rectus internus show such increased reflexive activity and such a strong tendency toward associated movements "When an effort is made," said Walsh and King, "to move the eye in any direction, impulses flow at the same time into all the muscles innervated by the third nerve Movement up or down does not occur, since the superior and the inferior rectus muscle contract together and the pull is balanced" "The tendency of the eye," said Ford and Woodhall, "to be adducted when other movements are attempted may be due to the fact that the action of the internal rectus is not opposed by synchronous contraction of the external rectus" This explanation is on a purely mechanical basis An impulse sent to any of the muscles innervated by the third nerve radiates to all muscles of this nerve and brings about their simultaneous contraction Those muscles innervated by the third nerve which are opposed by other muscles of this nerve will be counterbalanced, and no visible movement will result on their simultaneous innervation But those muscles controlled by the third nerve, which are opposed by muscles not innervated by other branches of the third nerve, will effect, through their unopposed action, displacement of the bulbus or of the eyelid

Against this hypothesis the following weighty objections may be raised 1 The usual associated movements may occur even when there

is no palsy of any muscle 2 The levator palpebrae muscle is unopposed by any muscle innervated by the third nerve But there are pathologic associated movements from the rectus internus to the levator palpebrae, whereas there are none from the rectus superior to the levator palpebrae The latter can be proved by the fact that when the patient closes his eyes and is asked to look upward the levator palpebrae does not move Thus, the unopposed levator palpebrae reacts differently according to whether the rectus internus or the rectus superior is innervated 3 There are no, or no distinct, associated movements from the levator palpebrae to other muscles In other words, the impulse sent to the levator does not radiate to all other muscles innervated by the third nerve 4 The single oculomotor muscles are by no means equally affected, and their action consequently cannot be completely balanced Partial movements are still possible, and in some muscles more so than in others 5 Associated movements are greater on looking downward than on looking upward This, again, shows that some other factor is at play here, not merely an even flow of impulses through all branches of the third nerve when a single branch has been stimulated For all these reasons it appears that the explanation of Ford and Woodhall is not tenable

The foregoing discussion serves to stress one fact the striking similarity between the condition due to lesions of the pyramidal tracts, as seen in cases of spastic paralysis, and the condition in the muscles of the third or the seventh nerve after partial recovery from palsy

ASSOCIATED MOVEMENTS AFTER LESIONS OF THE THIRD OR THE SEVENTH NERVE IN THE LIGHT OF THE RELEASE HYPOTHESIS OF HUGHLINGS JACKSON

Hughlings Jackson looked at the phenomena of spastic paralysis as release phenomena (*phénomène de relâchement, de libération,* of the French, *Enthemmungssymptom,* of the German) This brilliant hypothesis has proved extremely fruitful in the whole field of neurology, especially in the interpretation and elucidation of the phenomena that occur with lesions of the pyramidal tract After what has been said here on the symptomatology of third and of seventh nerve palsy, it is natural to attempt to apply Jackson's hypothesis to these phenomena as well It, then, must be assumed that an "escape from control" as it occurs in case of a lesion of the pyramidal tract takes place also with lesions of the third and the seventh nerve All the phenomena seen with the latter, i e, associated movements, muscle contractures and hyperreflexia, with their permanency and elements of phylogenetic retrogression, can be explained just as readily as they are with lesions of the pyramidal tract This hypothesis will also explain the difficulty encoun-

tered in the treatment of these conditions, since it is known how unmanageable is any condition which is a release phenomenon

There is one serious obstacle to the attempt to extend Jackson's hypothesis to the phenomena due to a central or a peripheral lesion of the third or the seventh nerve The third and seventh nerves are regarded as purely peripheral nerves, as is any spinal nerve originating from the anterior horns of the spinal cord Also, the nuclei of the third and seventh nerves are looked on as corresponding to a nucleus of the anterior horn However, this viewpoint calls for a change The peripheral neurons of the third and seventh nerves are different The motility in these nerves is regulated by centers which might be divided into nuclear, supranuclear, subcortical and cortical centers It must be assumed that, in contrast to the spinal nerves, the nuclear and closely neighboring supranuclear centers are more important for the movements of the muscles controlled by the third and seventh nerves than the anterior horns are for the movements of the muscles of the extremities The nuclear and supranuclear mechanisms of these two nerves are far more complicated and more independent of cortical and subcortical control than is the mechanism of a spinal nerve The nuclear and supranuclear mechanisms of the third and seventh nerves might represent for the respective muscles some combination of a pyramidal and a peripheral system, with the cerebral cortex exerting only a slight influence The significance which the pyramidal tract, the first neuron, has for the muscles of the extremities, the supranuclear and nuclear centers of the third and seventh nerves have for the ocular and facial muscles, a lesion of these centers produces phenomena analogous to the spastic paralysis seen with lesions of the first neuron In this connection it is worth while to mention "that there may be a localization of movement rather than individual muscles in the oculomotor nucleus" (Clark [114]), exactly as is found in the cortex

An injury to this peripheral, nuclear or supranuclear mechanism of these nerves has the same effect on the movement of the eyes and face, respectively, as a lesion of the pyramidal tract has on the movements of the extremities The lesion "knocks out" the frail, phylogenetically young mechanisms and thus releases phylogenetically older mechanisms, with their tendency toward associated movements Jackson propounded the theory that the highest and most lately developed functions suffer first in the process of disease, that the removal of the inhibition of these highest centers results in the uncontrolled action of the lower centers The assumption of existence of nuclear and supranuclear centers for the third and seventh nerves is of course highly hypothetic It might

114 Clark, W E L The Mammalian Oculomotor Nucleus, J Anat **60** 427, 1926

be less so if it is assumed that there exist in the nuclei types of cells of diversified physiologic dignity, as, for instance, in the striatum (Hunt[115]) The nuclei might contain phylogenetically younger, less resistant, physiologically highly differentiated cells, on the one side, and phylogenetically older, more resistant, physiologically less differentiated cells, on the other An injury to the third or the seventh nerve at any point in its course damages the weaker cells first, and associated movements result on partial recovery When both types of cells are damaged, no recovery and no hyperkinetic phenomena ensue

It is of course striking how readily associated movements appear in the area of the third and seventh nerves on the slightest injury This is due to the fact that the centers of this area, as of the whole area of the cranial nerves, carry, buried in their depths, a much more elaborate mass movement anlage than does any spinal nerve center This area is innately a playground for mass movements of many types The muscles of the eye and face have, even under normal conditions, a great tendency toward associated movements—this is especially true of the ocular muscles, and particularly of the levator palpebrae Some of these associated movements in the area of the third and seventh nerve are not directly pathologic but appear on the slightest deviation from the norm They are atavistic, dormant Their inhibitory, restraining mechanism is so frail, they are kept at bay so loosely, that they become discernible on the slightest provocation They appear also—and not uncommonly—as congenital anomalies Suffice it to mention here the Marcus Gunn phenomenon Some of these associated movements are on the physiologic borderline and appear in infants and especially in persons with motor infantilism, and they may appear even in normal persons The degree to which these tendencies toward associated movements are suppressed by the higher centers varies much from person to person Darwin[116] pointed out that some short-sighted people who contract their orbicularis oculi muscle when looking at distant objects raise their upper lip at the same time This is the most typical pathologic associated movement seen with lesions of the seventh nerve Coppez[117] made an interesting compilation of all the associated movements observed in the ocular muscles, which shows their tremendous variety under normal, as well as under pathologic, conditions All

115 Hunt, J R Progressive Atrophy of the Globus Pallidus, Tr Am Neurol A **43** 104, 1917

116 Darwin, C, cited by Collier, D J, in Discussion on the Limitations of Operative Treatment in Traumatic Facial Paralysis, Proc Roy Soc Med **34** 575, 1941

117 Coppez, H Essai de classification de quelques syncinesies oculaires, Rev d'oto-neuro-ocul **10** 12, 1932

this makes it understandable why the slightest lesion in the area of the ocular and facial muscles brings to light associated movements

The hypothesis presented here implies that the associated movements and other postparalytic motor manifestations in the areas of the third and seventh nerves are release phenomena, due to involvement of centers in the brain stem This hypothesis must now stand a severe test, i e, it must answer the following question How is it possible that these centers suffer when the lesion affects the trunk, or even the end branches, of the third or the seventh nerve? The answer is *réaction a distance,* as the French call it As far back as 1893, Darkschewitsch and Tichonow[118] demonstrated pathologic changes in the nucleus of the facial nerve after damage to the peripheral nerve In 1896 Flatau[119] found definite degeneration in the nucleus of the facial nerve in a case of peripheral palsy due to tuberculous otitis Vespa[120] observed degenerative changes in this nucleus, especially in its dorsomedial part, in a case of peripheral facial palsy of long standing with—and this is of particular interest—contractures and associated movements, as did Mirallie[120a] The same changes have been found with experimental lesions of the seventh nerve The medullary nucleus of the facial nerve, stated Sullivan,[121] does show histologic change in monkeys whose facial nerve has been cut and allowed to undergo degeneration for varying periods before being repaired As to the third nerve, Brouwer[60] described retrograde degeneration—though slight—in its motor nucleus after peripheral injury De Gutierrez-Mahoney[122] mentioned observations made by the method of retrograde reaction following intracranial division of the oculomotor nerve in the monkey, baboon and chimpanzee The retrograde reaction (chromatolysis) was noted in the homolateral motor cells and in some cells of the central nucleus of Perlia Van Gehuchten and van Biervliet[122a] reported similar experiments on rabbits Wilson[123]

118 Darkschewitsch, L, and Tichonow, S Zur Frage von den pathologisch-anatomischen Veranderungen bei peripherer Facialislahmung nichtspecifischen Ursprungs, Neurol Centralbl **12** 329, 1893

119 Flatau, E Pathologisch-anatomischer Befund bei einem Fall peripherischer Facialislahmung, Neurol Centralbl **15** 718, 1896

120 Vespa, B Studio sulle alterazioni del nucleo bulbare del faciale, in caso di antica paralisi periferica di questo nervo, Riv quindicin di psicol **2** 267, 1898-1899

120a Mirallie, C Paralysie faciale peripherique, Autopsie, Rev neurol **14** 702, 1906

121 Sullivan, J A, in discussion on Fowler, E P Abnormal Movements Following Injury to the Facial Nerve, J A M A **113** 1003 (Sept 9) 1939

122 de Gutierrez-Mahoney, C G, in discussion on Bender and Weinstein,[68] p 51

stated "The view that local irritation of a nerve-trunk causes some *réaction à distance* on the nucleus is not physiologically impossible" Elsewhere he stated "The underlying process in Bell's palsy consists of a simple parenchymatous toxi-degeneration, with *réaction à distance* on the nucleus" It is thus understandable that a lesion anywhere in the area of the third or the seventh nerve influences the nucleus, thus damaging the function of the frail, phylogenetically young superstructure, which controls fine, isolated movements This superstructure is responsible for the differentiation of muscle function If it is damaged, a "dedifferentiation" results, which is the essence of associated movements

The many objections raised here previously against the hypothesis of misdirection of fibers can easily be met in the light of the hypothesis of release phenomena, which places the origin of the associated movements not at the site of the peripheral lesion but in the nuclear structure, which is influenced by the distant lesion The associated movements occur, then, only in those lesions of the nerve which are severe enough to influence the nucleus from a distance The hypothesis of release phenomena does not deny the possible misdirection of fibers, especially after surgical injury to a nerve However, it does not hold this misdirection responsible for permanent associated movements and regards the role of misdirection as temporary or, at the most, as negligible in comparison with the tremendous impact engendered by the loss of control from the higher centers Associated movements are independent of the nature of the lesion and appear whether the lesion is surgical or nonsurgical, local or diffuse, since any lesion in the area of the third or the seventh nerve may, in its retrograde action, influence the nucleus, damage it and thus promote loss of control on the part of the higher, extremely susceptible, sensitive centers This hypothesis places the third and seventh nerves in a category distinct from the spinal nerves In view of the innate tendency of the normal third and seventh nerves—and of all cranial nerves—toward associated movements, active or dormant, and in view of their phylogenetic development, such an assumption is by no means unreasonable In the light of the hypothesis of the release phenomena, it is understandable why neighboring compartments do not intermingle readily, as had to be assumed on the basis of the hypothesis of misdirection, and why the participation of this or that muscle in the associated movements is not dependent on its particular response to voluntary innervation The salient point is that the selec-

122a van Gehuchten and van Biervliet Le noyau de l'oculomoteur commun, 16, 19 et 21 mois après la resection du nerf, Névraxe **2** 207, 1901

123 Wilson, S A K Neurology, London, Edward Arnold & Co, 1940, pp 405 and 1639

tion—so to speak—of the muscles for their participation in the associated movements is not decided on in the periphery, at the site of the damage and according to the lawless sprouting of the regenerating fibers, but in the nuclear mechanism, and here according to the phylogenetic point of view, in conformity with the law of survival of the fittest and simplest The nature of the injury, the state of the nuclear mechanism and the actual damage to the "final common path" may, of course, influence the clinical manifestations of the associated movements, but only to a minor degree Their tendency is dominant, and they assert themselves despite all obstacles

The predominant participation of the levator palpebrae and the rectus internus in associated movements is easily explained on the basis of the assumption that they are phylogenetically older muscles They subserve the most primitive movements necessary for the visual act opening of the eye and turning the eye inward to fixate a near object These muscles can be compared to the flexors of the leg which subserve the primitive reflex of withdrawal of flight In the manifestations of spinal automatism, the action of the flexors of the legs is also predominant In both conditions a loss of control accounts for the prominence of these movements Both with lesions of the third and seventh nerves and with lesions of the pyramidal tract there is no parallelism between the ensuing palsy and the tendency toward associated movements The latter may be very marked though the palsy be minimal With both lesions associated movements can occur as a congenital anomaly, as a persistent motor defect Some kind of motor infantilism may be present without, or with only a slight, impairment of the motor power of the affected muscles Associated movements in the facial or oculomotor muscles need time for their development—time until the peripheral injury affects the nucleus from a distance, and until the diaschisis passes over It is quite possible to assume that the "incubation period" within which the lesion could influence the nucleus in retrograde action would be shorter than the time it would take for the fibers to grow from the point of lesion to the periphery Since the hypothesis of release phenomena places the genesis of associated movements in the nucleus, their appearance with lesions of the nucleus is quite understandable The nuclear and supranuclear mechanisms of the third and seventh nerves are so delicate, their phylogenetically younger structure is so fragile, they are so easily deranged in their function, that associated movements which follow the damage to these mechanisms appear regardless of the nature or location of the lesion, unless, of course, the lesion is so mild and the damage so slight and easily repaired that no retrograde action on the nucleus takes place, or unless the entire mechanism of the third or the seventh nerve is destroyed, as in cases of severe acquired lesions

or of congenital malformations In the latter condition the palsy is complete and no associated movements appear The same is true of lesions of the pyramidal tract, there are no hyperkinetic phenomena of any kind if the whole motor system is destroyed According to Jackson's theory, destructive lesions do not cause positive symptoms, as living and active tissue is required for their production As there are numerous conditions with congenital insufficiency of the pyramidal tract, so also there may be congenital insufficiency in the motor mechanisms of the third and seventh nerves leading to associated movements, and to these only Cyclic or rhythmic oculomotor palsy could be explained in the light of this hypothesis as being due to sudden discharge in the higher centers of the third and seventh nerves, in the brain stem This leads to release phenomena on the part of the lower centers This is comparable to what is seen in cases of epilepsy, especially of so-called autonomic epilepsy The constant and persistent, almost monotonous, pattern seen with associated movements of the third and seventh nerves, and also with lesions of the pyramidal tract, is due to unrestricted activity of preserved and comparatively healthy, undamaged nerve centers, which continue to act according to their own characteristic physiologic function They remain, therefore, for life—unchanging and unchangeable—and are not amenable to therapeutic influence This is true of flexor spasm seen with pyramidal lesions, of associated movements occurring with palsies of the third and seventh nerves, as well as of any release phenomena referable to other systems of the cerebrospinal axis This general rule does not exclude the fact that in rare instances the damage inflicted by the peripheral lesion to the central station may be so mild that spontaneous recovery leading to the cessation of the associated movements can and does take place This occurred in case 2 of this series which, so far as I can discover, stands alone But it can also be assumed that these temporary associated movements, occurring during the process of recovery of an injury to the third or the seventh nerve, are not so rare They escape the notice of both the patient and the physician because of their mildness and transient character

It is easily understandable that, because of the intimate connection between the motor mechanisms of all the cranial nerves, and by virtue of the very strong natural, inherent tendency toward associated movements of all the muscles innervated by the cranial nerves, a disturbance in one necessarily brings about a disturbance and release phenomena in others Thus, associated movements between muscles of the oculomotor and the trigeminal nerves can be explained The remarkable frequency with which associated movements of the facial muscles are found in cases of cryptogenic hemifacial spasm points to a common site of origin and

reminds one of conditions due to damage of the pyramidal system in which pathologic associated movements may exist but in which voluntary movements are little affected

The hypothesis propounded here regarding the physiology of the associated movements of the facial and oculomotor muscles places the origin of these movements not in the nerve trunk at the site of the lesion, where misdirection of fibers could have taken place, but centrally, in the nucleus—in the nuclear or supranuclear mechanism This is practically a regression to the old theories promulgated by Hitzig [88] (1872), Fuchs [7] (1893), Gowers [124] (1895), Remak [125] (1898), Myerson [85] (1920) and others, who assumed "a state of irritation" in the nucleus of the third and the seventh nerve, respectively This theory was recently revived for the seventh nerve by Bittorf [75] and by Sullivan [126] It is interesting to note in this connection that Stein [111] regarded cyclic oculomotor palsy as an isolation phenomenon, the preserved isles of the nucleus being isolated from supranuclear influence and displaying their own automatism The only difference between the hypothesis propounded here and that of older authors is the view that the "state of irritation" is due to release of control

GUSTOLACRIMAL REFLEX

After partial recovery of the seventh nerve palsy, not only pathologic motor phenomena—which are the subject of this paper—but pathologic vasomotor and secretory phenomena appear For these, too, misdirection of regenerating secretory fibers has been regarded as "the simplest and most logical explanation" (Ford [127]) Russin [128] accepted Ford's view Lyle [38] said cautiously "A misdirection of regenerating fibers may be the cause" The most important of these vasomotor and secretory phenomena occurring after seventh nerve palsy are (1) the gustolacrimal reflex and (2) the auriculotemporal syndrome Both are not uncommon but, oddly enough, are not even mentioned in such a detailed work as Wilson's "Neurology"

The pathologic gustolacrimal reflex, which is usually transient, appears only in cases of peripheral facial palsy It consists of a flow

124 Gowers, W R Clinical Lectures on Diseases of the Nervous System, Philadelphia, P Blakiston's Son & Co, 1895, p 115

125 Remak, E Zur Pathogenese der nach abgelaufenen Facialislahmungen zuruckbleibenden Gesichtsmuskelzuckungen, Berl klin Wchnschr **35** 1144, 1898

126 Sullivan, J A A Modification of the Ballance-Duel Technique in the Treatment of Facial Paralysis, Tr Am. Acad Ophth **41** 282, 1936

127 Ford, F R Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy (Syndrome of Crocodile Tears), Arch Neurol & Psychiat **29** 1279 (June) 1933

128 Russin, L A Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy, J A M A **113** 2310 (Dec 23) 1939

of tears from the homolateral eye when gustatory stimuli reach the anterior part of the tongue This reflex is called the "symptom of crocodile tears" It is a reflex from the chorda tympani through the nervus petrosus superficialis major to the nervus lacrimalis This pathologic reflex appears with lesions of the facial nerve in the fallopian canal between the ganglion geniculi and the chorda tympani It comes to light after the gustatory disturbances in the anterior two thirds of the tongue have disappeared This reflex can be explained on the basis of a release of a phylogenetically old mechanism The lacrimation on gustatory stimulation is an axon reflex usually suppressed by a normally functioning facial nerve The old mechanism is still at play in man, but in a latent and restricted form Suffice it to remember the wet, fatty eye of some persons while eating This increased lacrimation occurs to a mild degree in normal persons also on urination and defecation Under pathologic conditions this flow of tears may increase to so great a degree that real "micturition under tears" takes place Since the arc of the axon reflex of lacrimation on gustatory stimulation ascends no higher than the ganglion geniculi, it is understandable that with a lesion of the facial nerve above this ganglion this reflex may be released, and thus intensive lacrimation on eating and chewing occurs Kaminsky,[129] Kroll[130] and Bing[131] saw in the gustolacrimal reflex a release phenomenon

AURICULOTEMPORAL SYNDROME

In the so-called auriculotemporal syndrome, seen after incomplete recovery from facial nerve palsy, and after some other conditions, there are redness and increased perspiration in the area corresponding approximately to that innervated by the auriculotemporal nerve This occurs when the patient eats bitter or sour food According to Kaminsky,[132] this phenomenon exists in latent form in normal persons and becomes conspicuous when lower peripheral centers and tracts are released Guttmann,[133] too, looks on the auriculotemporal syndrome as a release phenomenon He assumes that vasodilator and secretory fibers supplying the affected area of the face are released from sympathetic control through the primary lesion of the facial nerve Thus,

129 Kaminsky, S D Ueber das Syndrom der Krokodilstranen, Deutsche Ztschr f Nervenh **110** 151, 1929

130 Kroll, M Die neuropathologischen Syndrome, zugleich Differentialdiagnostik der Nervenkrankheiten, Berlin, Julius Springer, 1929, p 222

131 Bing, R Das Prinzip der "Enthemmung" in der Physiopathologie, Schweiz Arch f Neurol u Psychiat **32** 177, 1938

132 Kaminsky, S D Das "auriculo-temporale (Parotitis-) Syndrom" bei Syringomyelie, Deutsche Ztschr f Nervenh **109**·296, 1929

133 Guttmann L, Die Schweisssekretion des Menschen in ihren Beziehungen zum Nervensystem, Ztschr f d ges Neurol u Psychiat **135** 1, 1931

sympathetic disturbances, both vasomotor and secretory, occurring after incomplete recovery from peripheral nerve palsy can also be viewed as release phenomena

FACIAL SPASM

Going beyond the essential object of this study, namely, the pathophysiology of postparalytic phenomena of the third and seventh nerves, one finds it quite natural to apply the hypothesis of release to hyperkinetic phenomena of the seventh nerve which are not related to paralysis Among them, the facial spasm is outstanding, especially with regard to its frequency Wilson [134] stated

> Facial spasm may be cryptogenic or symptomatic, non- or postparalytic, uni- or bilateral, partial or total, tonic, clonic, tonico-clonic, or fibrillary Common though it is, both causation and pathogenesis are obscure, while pathological data are scanty and ambiguous

It is the so-called cryptogenic, nonparalytic facial spasm which is considered here The textbooks and monographs list an endless variety of pathologic conditions which can produce, secondarily, reflexively or otherwise, this facial spasm The problem of causation is treated here exactly as in the case of trigeminal neuralgia In medical practice it is different None of the numerous theoretic causes can be uncovered in most cases It is a matter of common experience that cases of facial spasm, especially those of middle life, belong to the so-called cryptogenic group I have seen many a patient in whom it was impossible to detect or even suspect, any cause of the facial spasm local or distant, internal, neurologic or psychiatric—and this even after year-long observation, including hospital observation, during which all pertinent clinical and laboratory studies had been applied The monosymptomatic spasm usually persists unabated, despite every conceivable treatment This course of facial spasm led many to abandon the unsatisfactory theory of peripheral reflexive irritation and to turn to that of central, nuclear origin One may go a step further and assume that in the so-called cryptogenic group some autochthonous degenerative process takes place in the facial nuclear or supranuclear mechanism, a process akin to that seen in paralysis agitans, torticollis and narcolepsy Hemilateral or bilateral facial spasm is then, so to speak, a torticollis of the facial muscles Such degeneration would release lower mechanisms, which remain intact The unrestricted, uninhibited activity of these healthy lower mechanisms documents itself in spastic contractions of the facial muscles

It is interesting to note the opinion of Babinski [26] (1905) on what he called "peripheral facial hemispasm" He emphasized that such a spasm does not occur with cortical lesions and incriminated a lesion

134 Wilson,[123] p 1647

of the facial nucleus The same view is held here, the spasm, however, being regarded not as the result of a direct irritation but as a release phenomenon The term "peripheral" used by Babinski to distinguish this spasm from that of cortical origin is misleading, and Bloch,[135] reviewing Babinski's article, rightly criticized it In the latest publication on facial spasm, Ehni and Woltman [136] expressed the view that the lesion lies in the nucleus of the facial nerve or in the proximal portion of the facial nerve

CONCLUSIONS

The primary purpose of this study is a critical analysis of the commonly accepted hypothesis that associated movements in the third nerve are due to a misdirection of regenerating fibers An attempt has been made to show that if these associated movements are regarded as a release phenomenon due to a central lesion all the pertinent clinical facts can be more readily understood

Of the manifold complex problems encountered during this study, only some of the associated movements among the external muscles of the third nerve have been discussed here A discussion of the associated movements of the pupil and of those between oculomotor and other muscles has been omitted One reason for this omission was that associated movements among the extrinsic muscles of the third nerve seem to be the cardinal symptom which offers a clue to the pathophysiologic understanding of the whole problem Another reason was that I did not feel competent to delve deeper into the complex and perplexing problem of the physiology of ocular movements, the study of which is, nowadays, a science in itself The famous ophthalmologist Bielschowsky devoted decades of his life to the problems of the motility of the eye The weak point of the present study is the fact that it is written by a neurologist who is, ophthalmologically speaking, a layman On the other hand, it may have been advantageous to have approached the problem from a neurologic angle, to have placed the emphasis on its physiologic aspect and to have coordinated the associated movements occurring with third nerve palsy with other neurologic manifestations, outside the neuro-ophthalmologic field

This study is not intended to solve completely the problem of associated movements or to explain every symptom ever described in every case of such phenomena It attempts only to hint at a possible new approach to the problem, and there is no intention of proving or disproving conclusively either of the hypotheses discussed The question is only which hypothesis lends itself more readily and with greater

135 Bloch, E, in review of Babinski,[26] Neurol Centralbl **25** 563, 1906

136 Ehni, G, and Woltman, H W Hemifacial Spasm Review of One Hundred and Six Cases, Arch Neurol & Psychiat **53** 205 (March) 1945

facility, with more justice to the facts, to a logical interpretation of the clinical observations, and which hypothesis is in closer accord with general neurophysiologic concepts The hypothesis of release phenomenon propounded here, though it may appear somewhat hazardous, seems to be a workable, expandable one, capable of providing further supporting argumentation It deserves to be used as a point of departure for future clinical, pathologic and physiologic investigations Charles Darwin once said "Without hypothesis, there can be no useful observation"

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TOXIC PSYCHOSES ASSOCIATED WITH ADMINISTRATION OF QUINACRINE

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EVER since quinacrine hydrochloride was introduced into the therapy of malaria, it has been considered a most valuable addition to the series of antimalarial drugs, owing to its well established effectiveness, together with its relatively low toxicity This evaluation of the drug has not changed, even though reports of toxic effects after therapeutic doses and, in particular, of mental disorders following treatment with the drug were described as early as 1933 In that year Conoley [1] gave an unpublished report on psychosis following treatment with quinacrine In 1934 Kingsbury,[2] utilizing observations of his own, as well as of others (Cameron,[3] Green,[4] Hoops,[5] McSwan,[6] Quaife[7]), collected a series of 12 cases of psychoses associated with quinacrine therapy, with the records available, which had been observed in the Malay States Six more cases were published by Banerjee [8] in 1936, from India Decherd,[9] in 1937, saw 1 case of toxic delirium with fatal outcome He made reference to another case, observed by Chopra and Abdul Wahed [10] In

From Gorgas Hospital, Ancon, Canal Zone

1 Conoley, O F, cited by Kingsbury [2]

2 Kingsbury, A N Psychoses in Cases of Malaria Following the Exhibition of Atebrin, Lancet **2** 979 (Nov 3) 1934

3 Cameron, I G, in discussion on Green [4a]

4 Green, R (*a*) Toxic Effects Associated with the Use of Atebrin, Malayan M J **9** 22 (March) 1934, (*b*) Lectures on the Development and Use of the Synthetic Antimalarial Drugs, Bull Inst M Research, Federated Malay States, 1934, no 2, pp 1-50

5 Hoops, A L, in discussion on Green [4a]

6 McSwan, D M, cited by Kingsbury [2]

7 Quaife, W T, in discussion on Green [4a]

8 Banerjee, K. (*a*) Some Unnatural Phenomena in the Course of Atebrin Treatment, Calcutta M. J **30**:515 (March) 1936, (*b*) Two Cases of Poisoning After Injection of Atebrin Mussonate, ibid **31** 41 (July) 1936

9 Decherd, G M, Jr A Fatality After Atebrin-Plasmochin Treatment of Malaria, J Trop Med **40**·90 (April 15) 1937

10 Chopra, R N, and Abdul Wahed, A K M Toxic Effects Produced by Combined Treatment with Atebrin and Plasmochin, Indian M Gaz **69** 213 (April) 1934

the same year Allen, Allen and Fulghum [11] published a series of 9 cases In 1938 another observation was reported by Bispham [12] The same author,[13] in 1941, surveyed the literature up to that date and mentioned 7 more cases reported by Udalagama [14] from Ceylon in 1935 This paper is inaccessible to us Other case reports equally inaccessible were cited by Choremis and Spiliopoulos [15] 1 each of Kang and Jarvis,[16] from China (1936), and Govindaswami,[17] from India (1936) Briercliffe [18] (1935) saw psychotic disturbances during the great epidemic of malaria in Ceylon In 1941 Lerro [19] published a case of quinacrine psychosis observed in Panama, and Wilkinson [20] described 3 cases

While it is not at all certain that all the observations mentioned may rightly be labeled cases of quinacrine psychosis, and while, on the other hand, single case reports scattered through the huge literature on malaria may have escaped our attention, it is probably justified to consider the figure of 43 cases of quinacrine psychoses observed hitherto—the sum total of the aforementioned reported cases—as a rough estimate of the total incidence of such cases in the literature In view of the comparative rarity of the condition, it appears worth while to publish a series of 19 cases of quinacrine psychosis which have been observed during the last eight years—1935 to 1943—ever since quinacrine therapy was instituted in Gorgas Hospital Our series of cases is summarized in the table accompanying this article

The neurologic after-effects of treatment with quinacrine are still less frequent than the psychoses They seem to occur particularly in small children and consist in acute forms of polyneuritis or myeloradiculo-

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11 Allen, E W , Allen, H D , Jr , and Fulghum, C B Psychosis Following the Administration of Atabrine for Malaria, J M A Georgia **26** 62 (Feb) 1937

12 Bispham, W N Final Report on the Use of Atabrine in the Prophylaxis and Treatment of Malaria, Am J Trop Med **18** 545 (Sept) 1938

13 Bispham, W N Toxic Reactions Following the Use of Atabrine in Malaria, Am J Trop Med **21** 455 (May) 1941

14 Udalagama, L Mental Derangement in Malaria Cases Treated with Atebrin-Mussonate Injections, Indian M Gaz **70** 679 (Dec) 1935

15 Choremis, K , and Spiliopoulos, G Paralytische Erscheinungen nach Gebrauch von synthetischen Antimalaria-Mitteln, Deutsche med Wchnschr **64** 1680 (Nov 18) 1938

16 Kang, T , and Jarvis, B W Maniacal Symptoms Following the Use of Atebrin, Chinese M J **50** 976 (July) 1936

17 Govindaswami, M V Atebrin Poisoning, Lancet **1** 56 (Jan 4) 1936

18 Briercliffe, R The Ceylon Malaria Epidemic, 1934-35 Report by the Director of Medical and Sanitary Services, Colombo, Ceylon Government Press, September 1935

19 Lerro, S J Report of Two Cases of Toxicity to Atabrine, Mil Surgeon **89** 668 (Oct) 1941

20 Wilkinson, P B Mental Disturbance After the Exhibition of Atebrin, Caduceus **18** 267 (Nov) 1939

neuritis Two cases have been reported in the Italian literature (Moschini,[21] 1935, and Valentini,[22] 1937) and a series of 5 cases in the German literature (Choremis and Spiliopoulos,[15] 1938) The latter observers refei red to Castellani and Chalmers,[23] who observed similar neurologic pictures in patients with chronic malaria who were cured by ti eatment with quinine In view of the fact that all the reported cases of polyneuritis in children occurred with chronic malai ia, the etiologic part played by quinacrine cannot very well be estimated

With regard to observations on adults, case 2 reported by Lerro [19] deserves to be mentioned, in this case treatment with quinaci ine was followed by paresthesias over the entire body, associated with nausea, vomiting and a choking sensation In view of the fact that in animal experiments quinacrine in toxic doses causes clonic convulsions (Molitor [24]), the occurrence of epileptiform fits after treatment with the drug mentioned by Stitt [25] (in cases of Field and Niven,[26] Vardy [27] and van Heukelom and Overbeek [28]) is of interest

INCIDENCE

The total number of cases in Gorgas Hospital in which quinaci ine treatment was employed during the period from May 1935 to November 1943 was 4,876, of which 2,653 were cases of tertian malaria and 2,223 cases of estivoautumnal malaria The few cases of mixed infection have not been counted separately but are included in these figures Quinacrine hydrochloride was usually given in conjunction with quinine or pamaquine naphthoate However, quinacrine was, in these cases, the

21 Moschini, S Polineurite cerebrospinale acuta motoria, di natura tossica, ad inizio apoplettiforme in una bambina di due anni, Riv di clin pediat **33** 823 (July) 1935

22 Valentini, P A proposito di una grave sindrome mielo-radicolo-neuritica insorta nel corso di terapia atebrinica, Pediatria **45** 51 (Jan) 1937

23 Castellani, A , and Chalmers, A J Manual of Tropical Medicine, ed 3, London, Bailliere, Tindall & Cox, 1919, pp 1175-1176

24 Molitor, H Antimalarials Other than Quinine, in Moulton, F R A Symposium on Human Malaria with Special Reference to North America and the Caribbean Region, Publication 15, American Association for the Advancement of Science, 1941

25 Strong, R P Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed 6, Philadelphia, The Blakiston Company, 1942

26 Field, J W , and Niven, J C Clinical Comparison of Atebrin Mussonate with Quinine Bihydrochloride, Tr Roy Soc Trop Med & Hyg **29** 647 (April 8) 1936

27 Vardy, E C Notes on a Clinical Investigation of the Treatment of Malaria by Atebrin Mussonate Injections, Malayan M J **10** 67 (Sept) 1935

28 van Heukelom, A S , and Overbeek, J G The Treatment of Acute Malaria with Atebrin Injections, Geneesk tijdschr v Nederl -Indie **76** 2507 (Oct) 1936

principal antimalarial drug, and quinine and pamaquine naphthoate were used in follow-up treatment The average dose of quinacrine hydrochloride used was 1 7 to 1 8 Gm, given over the course of five to six days, and only in a negligible number of cases did it exceed 2 1 Gm

We observed 19 cases of quinacrine psychosis The incidence, therefore, was 0 39 per cent, or about 1 out of 250 cases In order to calculate the incidence for estivoautumnal and tertian malaria separately, we have to eliminate 6 of our 19 cases, because in 3 of them the type of parasite was unknown, in 2 cases there was mixed estivoautumnal and tertian infection and 1 was a case of quartan malaria For the proportionately reduced total number of cases of estivoautumnal and tertian malaria treated with quinacrine, the incidence of psychosis for the two types of malaria was 0 46 and 0 33 per cent, respectively, and therefore somewhat higher for estivoautumnal than for tertian malaria

The incidence as given in the literature varies considerably

Kingsbury [2]	12 "among several thousand"
Bispham [12]	1 in 422 cases
Green [4]	2 in 750 cases
Allen Jr [29]	1 in 2,000 cases (estimate)
Udalagama [14]	7 in 644 cases

The only exact figures are those of Bispham,[12] Green [4] and Udalagama [14] The high incidence found by the last author is explained by two facts (1) He used intramuscular injections of quinacrine mussonate, a method which seems to be more toxic than the usual oral administration of quinacrine hydrochloride, (2) his observations also include states of depression following treatment with quinacrine, and it is doubtful whether these can be counted as true quinacrine psychoses The figures of Bispham [12] and Green [4] would be equivalent to 0 24 and 0 27 per cent, respectively, values considerably lower than ours However, their material (1 and 2 cases, respectively) is obviously too small for comparison

SYMPTOMS

To illustrate the clinical picture of quinacrine psychosis, a typical case will be reported in brief

Case 13.—A white American, a man aged 36, was admitted to Gorgas Hospital on Nov 5, 1942, with mixed tertian and estivoautumnal malaria He was placed under quinacrine therapy and given 0 2 Gm of the drug intramuscularly, followed by oral administration of 0 1 Gm three times a day On the night of November 12, after an intake of 2 Gm of quinacrine hydrochloride within six days, he suddenly became confused, irrational and resistive and would not stay in bed He still had fever on that day, however, the last time that the parasites of estivoautumnal and tertian malaria had been found in his blood was five and four days, respectively, prior to the outbreak of his psychosis The following morning he became noisy, excited and talkative and began throwing bedside articles about the ward It became necessary to put him in a seclusion room.

29 Allen, H D, Jr, in discussion on Allen, Allen and Fulghum [11]

Quinacrine therapy was immediately discontinued, and he was placed under treatment with quinine, increased intake of fluid and high doses of vitamin B complex, including parenteral injections of thiamine hydrochloride He soon quieted down, and on November 14 he was mentally clear, rational and oriented

This patient exhibited, immediately after an attack of mixed tertian and estivoautumnal malaria, and at the end of a course of a total 2 Gm of quinacrine hydrochloride, an acute psychosis, with all the characteristics of an organic reaction type confusion, restlessness, pronounced psychomotor excitement, destructiveness, increased pressure of speech and clouded sensorium The psychosis subsided almost as suddenly as it had developed, after little more than one day's duration

In most of our cases (e g, cases 2, 3, 10 and 12), essentially the same psychopathologic picture, with minor variations, was exhibited Usually the emotional factor seems to be predominant, producing the syndrome of confused mania or that of anxiety psychosis or panic, in other cases, catatonic features are noticeable (cases 1, 5, 6 and 15), again, there are cases with prominent paranoid content (cases 7, 9 and 14), visual and auditory hallucinations may dominate the picture (cases 9, 11 and 16), and, finally, a full blown toxic delirium may be present (cases 4 and 15)

There is nothing specific in the psychiatric symptoms of the quinacrine psychosis It corresponds to the well known type of toxic psychosis of various causes, most frequently seen subsequent to endotoxic processes, such as hyperthyroidism, or nutritional deficiency, such as pellagra or other forms of B avitaminosis Neurologic examination almost invariably revealed nothing abnormal, which goes to prove that the condition is not due to any localized pathologic process of encephalitic character The variations mentioned—manic, catatonic, paranoid and hallucinatory—are most likely due to differences in the prepsychotic personality structure

Unusual clinical features develop in cases in which quinacrine psychosis is superimposed on some organic pathologic process in the brain This occurred in 2 cases in our series, which therefore deserve to be reported separately

Case 8—A white American man aged 22 was transferred on July 10, 1942 to Gorgas Hospital from an outlying hospital, where he had been under treatment for malaria since May 30, 1942 On May 31, 1942 his blood smear revealed parasites of estivoautumnal malaria He was placed on routine quinine therapy, followed by a course of quinacrine treatment The total dose of the drug could not be ascertained On July 6, 1942 a blood smear was found positive for trophozoites of tertian malaria Again, he was placed on quinacrine therapy, the dose being unknown At that time he began to exhibit mental symptoms, manifested by vague and irrelevant conversation, bewilderment and confusion Because of his mental condition, he was transferred to Gorgas Hospital At that time, his tem-

perature was normal and his blood negative for malaria organisms He was confused, disoriented, perplexed, mentally retarded and hesitant in speech and showed impairment of recent memory The sensorium was clouded The skin and scleras were lemon yellow Neurologic examination revealed nothing abnormal Under treatment with forced intake of fluids, large amounts of vitamin B complex and parenteral injection of thiamine hydrochloride, he began to show improvement On July 24, 1942 his mental state appeared entirely clear After the psychosis had subsided, however, he was noted to be slow in grasping ideas and seemed intellectually retarded His past personal history revealed that he had always been slow to learn, had to be shown repeatedly how to perform certain duties and was mentally below average His mentality was estimated to be that of a medium grade moron He was discharged from the hospital on August 2 as recovered from malaria and the toxic psychosis

While the history in this case left hardly any doubt that quinacrine was the main causative factor, the psychiatric picture differed considerably from the usual pattern Instead of the hyperactivity and psychomotor excitation usually seen, the patient appeared retarded and bewildered and exhibited impairment of recent memory His psychosis lacked productivity, hallucinations, delusions, and pathologic impulses being entirely absent Another relevant fact distinguishing this case from most of our series is that though quinacrine therapy was immediately discontinued and the routine vitamin treatment given it took eighteen days for the psychosis to clear up The theory that the atypical picture and course of the toxic psychosis in this case were due to its being superimposed on an organic cerebral defectiveness is, though not conclusive, highly suggestive It appears to be just a special case in kind of the prepsychotic personality modeling and modifying the structure of a psychosis, except that with mental deficiency the preexisting personality is so basically different from the average that, as a result of the toxic process going on in an already abnormal brain, an altogether atypical picture develops

Case 6.—A Salvadorian man aged 39 was admitted to Gorgas Hospital on July 5, 1942, with a temperature of 102 F and a blood smear positive for the parasites of estivoautumnal malaria He was placed on quinacrine therapy, receiving 0 6 Gm daily for four days, or a total of 2 4 Gm On the second day of hospitalization his temperature dropped to normal The last blood smear which was positive for parasites of estivoautumnal malaria was taken on July 6 During the night of July 9 he suddenly became disturbed, yelling, screaming and thrashing about in his bed Seclusion and sedation were necessary Next morning he still was acutely excited, disturbed, hyperactive and catatonic He would assume a prayerful attitude for one minute and the next minute go through numerous bizarre mannerisms All tendon reflexes were exaggerated The patient was placed on a regimen of high fluid intake, sedation, parenteral administration of thiamine hydrochloride and oral use of vitamin B complex On July 8 the Wassermann reaction of the blood was negative, and the Kahn reaction was a doubtful 1 plus Examination of the spinal fluid, on July 14, revealed a 2 plus Wassermann reaction, 1 plus reactions in the ammonium sulfate and phenol tests and a colloidal

gold curve of 5555421100 The cell count was 0 During the following weeks, the patient had a temperature ranging from 100 to 104 F He remained in a state of delirium, talking or muttering incessantly, was hyperactive, excited and resistive and had to be kept in restraint in spite of sedation with paraldehyde and sodium amytal Examinations of the blood, when repeated, showed the same reactions After the Wassermann reaction of the spinal fluid had been reported as 2 plus, treatment was started with graduated doses of potassium iodide and bismuth subsalicylate in oil, 0 13 Gm given intramuscularly once a week The patient's mental condition showed no improvement, and the course was progressively downhill He died on August 10, with a terminal temperature of 108 F

Autopsy (significant observations only)—The body was that of a moderately emaciated, asthenic, brown Salvadorian The left pupil measured 0 7 cm and the right 0 5 cm The lips were pale and cyanotic The gums had a blue color around the base of the teeth The mucous membrane of the mouth was pale Small, "shotty" lymph nodes were palpable in the axillary and inguinal regions Scattered over the back, shoulders and neck was a fine papular eruption There was a small decubital ulcer over the tip of the sacrum The nails appeared faintly cyanotic The dura appeared slightly thickened but could be stripped from the skull without great difficulty Cerebrospinal fluid withdrawn by cisternal puncture was clear and yellow The meninges over the entire cerebrum appeared thickened Particularly along the midline this thickening assumed the form of numerous fine granulations, resembling pacchionian granules but somewhat more diffuse The sulci were slightly widened, and the meninges filling the sulci appeared to have small patches of scarring, averaging 0 3 cm in diameter The blood vessels of the meninges appeared grossly dilated

The brain was relatively firm and retained its contour well in sectioning Its weight was 1,330 Gm The vessels within the parenchyma of the brain stood out prominently, as though moderately congested The ependyma of the lateral and fourth ventricles showed minimal roughening but no granulation

The lymphoid follicles at the base of the tongue were moderately enlarged The larynx, trachea and bronchi were filled with frothy, white, slightly blood-tinged serous fluid The mucous membrane of the lower part of the trachea and the bronchi was greatly congested Approximately 15 cc of fluid lay within the left pleural cavity The right pleural cavity was completely obliterated by firm fibrous adhesions, binding all faces of the lung to the parietal pleura The upper lobe of the left lung was pale pink, soft and crepitant The lower lobe of the left lung was firm and reddish purple with areas of bluish discoloration On section the upper lobe appeared light red The lower lobe was dark red, and serosanguineous fluid could be expressed from the bronchioles The right lung was relatively firm but slightly crepitant On section the lung appeared dark red, and serosanguineous fluid could be expressed from its bronchioles The heart muscle was dark brown and felt somewhat flabby The aortic valve had a small plaque of calcification in the right cusp The ascending portion, the arch and the proximal portion of the descending part of the thoracic aorta showed pronounced thickening and wrinkling, forming deep longitudinal corrugations Little sclerosis was present Most of these corrugations appeared to be due to fibrous scarring This condition was most pronounced in the ascending portion of the aorta, where there was an area of apparent dilatation, starting 2 cm from the aortic valve These corrugations extended to the ostiums of the coronary arteries but not into these vessels themselves The liver appeared somewhat enlarged and weighed 1,780 Gm The surface and the cut sections were reddish brown, scattered through them were numerous small areas of light yellow, measuring approximately 0 5 cm in diameter

Data on Nineteen Cases of Quinacrine Psychoses Occurring at Gorgas Hospital from 1935 to 1943

Case Sex, Age	Race	Type of Malaria *	Dose of Quinacrine at Start of Psychosis, Gm	Days Elapsed Between Start of Psychosis and: Last Fever	Last Positive Smear	Last Dose of Quinacrine	Duration of Psychosis, Days	Symptoms	Treatment	Outcome and Comments
1 F 45	Foreign white	E A	1 5	2	0	0	32	Patient noisy, disturbed, restless, confused, removing clothes, later filthy, smearing feces, resistive, unmanageable	Sedation	Recovery Quinacrine had been continued for one week after outbreak of psychosis, up to total dosage of 3 6 Gm
2 F 45	Negro	E A	1 8	2	2	1	4	Patient noisy, screaming, crying, talking incoherently, throwing objects around, confused	Sedation, quinine, ovarian tablets	Recovery
3 M 30	White American	F U O	1 9	1	Smear always negative	0	1½	Patient irrational, noisy, crying, surly, mumbling incoherently to himself, confused, restless, emotional	Sedation	Recovery
4 M 26	Foreign white	Tertian	3 0	10	8	2	13	Toxic delirium, patient hyperactive, excited, muttering	Sedation, quinine, fluids, vitamin B	Death Lemon yellow skin, albuminuria, casts, leukocytes 9,000-20,000, cultures of spinal fluid and blood sterile
5 M 19	Foreign white	E A	1 8	0	2	0	2	Patient confused, uncooperative, catatonic, clouded sensorium	Fluids, vitamin B, sedation	Recovery
6 M 39	Foreign white	E A	2 4	3	3	0	31	Patient disturbed, screaming, excited, hyperactive, catatonic, bizarre mannerism, delirious, temperature up to 103 F	Antisyphilitic treatment, vitamin B	Death Autopsy, diagnosis, dementia paralytica
7 M 31	White American	Quartan	Unknown	Unknown	Unknown	Unknown	3	Patient confused, disoriented paranoid, visual hallucinations	Quinine, sedation, vitamin B	Recovery Yellow tinged skin
8 M 22	White American	E A, tertian	Unknown	Unknown	1 2 days for tertian	0	18	Vague, irrelevent talk, patient bewildered, confused, uncooperative, retarded, clouded sensorium, impairment of recent memory	Vitamin B	Recovery Yellow skin, medium grade moron

9 M 31	Foreign white	Tertian	18	3	4	0	2	Patient excited, suspicious, auditory and visual hallucinations, apprehensive, paranoid, depressive delusions	Vitamin B, sedation, quinine	Recovery
10 M 28	White American	Unknown	57	Unknown	Unknown	1	2½	Patient violent, confused, excited, apprehensive, destructive, mumbling, incoherent speech, bilateral ankle clonus	Saline and dextrose solution, sedation, vitamin B	Recovery Lemon yellow skin
11 M 22	White American	Tertian	22 (0 2 i m)	2	0	3	1	Patient excited, violent, auditory and visual hallucinations, delusions of grandeur	Sedation, vitamin B	Recovery Tertian parasites in blood until 11th day
12 M 24	Foreign white	F U O	16	1	Always negative	0	2	Patient apprehensive, talking incessantly, violent, confused	Sedation, vitamin B	Recovery
13 M 36	White American	Tertian, E A	20 (0 2 i m)	0	4	0	1	Patient confused, irrational, resistive, noisy, excited, talkative, throwing objects around	Sedation, dextrose saline solution, vitamin B	Recovery
14 M 33	White American	Tertian	11	0	0	0	1	Patient confused, disoriented, irrational, delusional	Quinine, dextrose, sedation	Recovery
15 M 16	Negro	Tertian	17	6	5	0	6	Patient wild, violent, noisy, disoriented, auditory hallucinations, clouded sensorium, temperature 100 F	Sedation, vitamin B	Recovery Psychosis lasted 6 days, cleared up 1 day after vitamin B therapy was started
16 M 28	White American	F A	09	0	0	0	7	Patient confused, bewildered, disoriented, auditory hallucinations, clouded sensorium, temperature 100 F	Sedation, dextrose saline solution, vitamin B	Recovery Scleras yellow, psychosis, lasting 5 days, cleared up 12 days after vitamin B therapy was started
17 M 23	White American	E A	15	5	Unknown	5	20	Patient confused, hyperactive, loss of recent memory, loss of inhibitions	Vitamin B, sedation	Recovery
18 M 25	Foreign white	F A	05 (0 2 i v)	0	0	0	½	Manic excitement, patient confused, hyperactive	Sedation	Recovery Psychosis started 1½ hours after intravenous administration of 0 2 Gm quinacrine hydrochloride
19 M 29	Foreign white	Tertian	19	Unknown	Unknown	0	14	Patient very talkative, noisy, emotionally unstable	Vitamin B, sedation	Recovery

* F A indicates estivoautumnal malaria, F U O, fever, undetermined origin

and resembling focal fatty degeneration The spleen measured 14 by 7 by 3 cm and weighed 165 Gm The capsule appeared thickened The trabecular markings were unusually prominent The smooth surface of the kidneys showed scattered dark brown, depressed areas The pelves appeared slightly thickened and congested and contained purulent material In the esophagus there were two areas of ulceration, measuring 3 by 1 and 1 5 by 0 5 cm, respectively These ulcerations were apparently produced by an in-dwelling stomach tube, which was needed to feed the patient The gastric mucosa showed a few scattered petechial hemorrhages Moderate congestion and apparent petechial hemorrhages were present in the sigmoid and rectum A single female ascarid was found in the colon

Microscopic Examination of the Brain—The leptomeninges were composed of fairly heavy strands of connective tissue, with moderate lymphocytic infiltration The vessels of the meninges were engorged with blood In the ganglion cells of the frontal cortex the Nissl substance was lacking A moderate amount of fine, yellow granular material, resembling lipid pigment, was present within the cytoplasmic portion of the cells A few of the blood vessels appeared to have undergone disruption and extravasation of red cells into the nerve tissue There was slight lymphocytic infiltration in the Virchow-Robin spaces The ependyma of the fourth ventricle was made up of a regular layer of small cells with occasional small patches of subependymal glial proliferation

Anatomic Diagnosis—The diagnosis was syphilitic meningoencephalitis, a few focal hemorrhages of the cerebral cortex, bronchopneumonia and syphilitic and arteriosclerotic aortitis

In this case a toxic psychosis developed after a course of 2 4 Gm of quinacrine hydrochloride, superimposed on undiagnosed dementia paralytica As can be seen from the autopsy report, the process of syphilitic meningoencephalitis appears to have been in a rather early stage and not very active, as was also demonstrated by an only doubtfully positive Kahn reaction of the blood and the absence of cells in the spinal fluid Nevertheless, the disease seems to have been sufficiently advanced to produce, in combination with the toxic effect of quinacrine, a severe, fatal delirium, of thirty-two days' duration While it is true that fulminant dementia paralytica may occasionally show rapid progression toward death, the clinicopathologic and autopsy observations in our case would hardly be consistent with such a course On the other hand, it is known that quinacrine psychosis is usually benign and of short duration It appears, therefore, justified to attribute the peculiar clinical picture and fatal outcome in this case to the deleterious effect of quinacrine on a brain which was already diseased with early dementia paralytica

The symptoms of quinacrine psychosis, as described in the literature, essentially agree with our observations States of manic or hypomanic excitement seem to be most frequent (Kang and Jarvis [16], Bispham [12], Allen, Allen and Fulghum [11]) Probably those cases labeled instances of "cerebral excitation" by early observers (Conoley,[1] Hoops,[5] McSwan,[6] Green [4]) belong in the same category The occurrence of delirium has been reported by Govindaswami,[17] Decherd [9] and Lerro [19] In a case reported by Kingsbury [2] visual hallucinations were prevalent in an

otherwise catatonic condition A schizophrenia-like psychosis was observed by Banerjee [8b], a paranoid syndrome, by the latter and by Cameron [3] In cases of Allen, Allen and Fulghum [11] and of Kingsbury [2] confusional states were present We did not observe depressive conditions, such as were described by Kingsbury,[2] Banerjee,[8a] Bispham [12] and Quaife [7] We did not see, either, cases of prolonged coma, as mentioned by Beckman [30]

ONSET, COURSE, DURATION AND OUTCOME

Quinacrine psychoses start usually, though not always, after the fever caused by malaria has subsided and no more parasites are found in the blood As can be seen in our table, the time intervals between the last day of fever and the onset of the psychosis were, in those cases in which exact data were available, as follows

No of Days	No of Cases
0	5
1	2
2	3
3	2
5	1
6	1
10	1

The average interval was 2 2 days, the median, 2 days The time intervals between the last positive blood smear and the onset of the psychosis were distributed as follows

No of Days	No of Cases
0	4
1	1
2	3
3	1
4	2
5	2
8	1

The average interval was 2 6 days, the median, 2 days As to the relationship between the termination of administration of quinacrine and the onset of the psychosis, in most of our cases quinacrine was discontinued only when psychotic symptoms occurred (in 12 out of 17 cases in which data were available) Usually it was the same day on which the course of quinacrine therapy had been, or was to be, terminated anyway However, there were 2 cases in which one day elapsed between the last dose of quinacrine and the onset of the psychosis and 3 cases in which the

30 Beckman, H Treatment in General Practice, ed 4, Philadelphia, W B Saunders Company, 1942, p 97

intervals were two, three and five days, respectively In 1 case—the first in our series, observed at a time when quinacrine as a possible cause of mental disorder was not yet considered by the observers in Gorgas Hospital—treatment with the drug was continued after the outbreak of the psychosis, up to a total dose of 3 6 Gm The psychosis lasted thirty-two days

The onset is usually sudden, but it may be gradual, preceded by a short period—one day or less—of nervousness, malaise, restlessness or insomnia The psychosis develops, in most cases, to a climax within one day or less, remains at its height for a variable length of time and is followed by rapid recovery Its duration in our series was as follows

Duration, Days	No of Cases
1 or less	3
1½	2
2	3
2½	1
3	1
4	1
6	1
7	1
13 *	1
14	1
18	1
20	1
31 *	1
32 †	1

* Fatal outcome

† In this case, quinacrine therapy had been continued for another week after the psychosis had started

The average duration of the psychosis in those cases in which the outcome was recovery was 8 5 days, the median duration, 2 5 days

The outcome of quinacrine psychosis is almost invariably complete recovery However, in addition to the fatal case of quinacrine psychosis with dementia paralytica, just reported, we observed another fatal case which deserves to be reported in some detail

Case 4—A Puerto Rican man aged 26 was admitted to Gorgas Hospital on Feb 25, 1943, as a transfer from an outlying hospital He had been admitted to the latter on February 5, with a temperature of 99 2 F and a history of chills, fever, headache and profuse sweating, of one day's duration On February 6 the smear was positive for trophozoites of tertian malaria He received an initial dose of 3 Gm of quinine sulfate, followed by 0 66 Gm three times a day for five days, then quinacrine hydrochloride, 0 1 Gm three times a day for ten days (a total of 3 Gm), then quinine sulfate, 0 66 Gm , three times a day for five days The course of his illness

was afebrile after the first day and was uneventful except for a furuncle in the right axilla, which was incised and drained on February 13 A smear on February 18 was negative for malarial organisms The patient was to be discharged on February 25, when it was noticed that his behavior was peculiar It was learned from the chaplain that he had noted some mental aberration a few days previously, or about two days after the completion of the course of quinacrine therapy On admission to Gorgas Hospital, the patient's temperature was 101 6 F The blood count was 70 per cent hemoglobin, 3,950,000 red cells and 11,400 white cells, with a differential count of 72 per cent neutrophils and 28 per cent lymphocytes The general physical examination revealed nothing significant except for lemon yellow discoloration of the skin and scleras Mentally the patient exhibited the picture of toxic delirium, with marked hyperactivity, excitement and constant muttering He had to be controlled with sedatives On February 27 his temperature rose to 104 8 F, and, although all smears were negative for the parasites, it was considered advisable to place him under treatment with quinine sulfate Treatment with forced intake of fluids, high doses of vitamin B complex and thiamine hydrochloride had already been given Examination of the spinal fluid on February 27 revealed 5 lymphocytes per cubic centimeter, 0 02 Gm of protein per hundred cubic centimeters, negative serologic reactions and a normal colloidal gold curve The temperature rose to 106 6 F (rectally) A roentgenogram of the chest, taken on March 1, revealed a small patch of pneumonitis in the middle portion of the right lung He was placed under treatment with sulfadiazine, with an initial dose of 6 Gm and a maintenance dose of 1 0 Gm every four hours Examination of the spinal fluid on March 1 showed 5 lymphocytes per cubic millimeter, 119 mg of glucose per hundred cubic centimeters, 800 mg of sodium chloride and 0 031 Gm of protein per hundred cubic centimeters, negative serologic reactions, a normal colloidal gold curve and sterile cultures Repeated blood cultures were sterile, the albumin-globulin ratio, fasting blood chemistry and icteric index were normal, and agglutination tests for typhoid, paratyphoid and brucellosis were negative Repeated specimens of urine showed a trace to a 2 plus reaction for albumin, a few pus cells, occasional red cells and granular and hyaline casts Examination revealed no tyrosine crystals The white blood cell count ranged from 9,200 to 20,000 and the differential count, from 78 neutrophils, 5 eosinophils and 17 lymphocytes to 57 neutrophils, 3 myelocytes 1 eosinophil and 37 lymphocytes, per hundred cells On March 2 the patient showed temporary improvement, which continued until March 3, when his temperature rose to 103 F, and he again became noisy, restless and disturbed From this day his course was progressively downhill, until he died on March 7

Autopsy (March 7, significant observations only) —The brain weighed 1,350 Gm The leptomeninges and parenchyma were slightly congested Lymphoid follicles at the base of the tongue were prominent The heart was slightly larger than usual The liver was distinctly enlarged, weighing 2,500 Gm The parenchyma was firm, dark red and bloody and appeared somewhat swollen, tending to bulge above the cut surface The spleen was enlarged, weighing 370 Gm The parenchyma was firm, dark red and rubbery On the cut surface of the kidneys there could be seen within the cortices barely visible glomeruli, which stood out as tiny shiny spots Within the jejunum there were found 4 worms of the species N americanus

Microscopic Examination —Brain A small amount of granular, eosinophilic material was present in the subarachnoid space The nuclei of the nerve cells were possibly slightly hyperchromatic

Liver The venous sinuses in all portions of the lobules were distended with blood The cytoplasmic borders were rather indistinct The cells of Kupffer contained a moderate amount of yellowish black pigment, most of which appeared to be malaria pigment

Spleen The malpighian corpuscles were rather large, with prominent germinal centers The venous sinuses were congested, and the follicles stood out prominently against this reddish background Only a small amount of pigment was present within the spleen

Kidneys The glomeruli were rather large, and the loops were stuffed with blood, so that each capillary appeared swollen The lumens of some of the tubules contained a small amount of amorphous eosinophilic material Only a rare tubule contained an albuminous cast

Prostate Gland The lumen of practically every acinus was packed with pus and cellular debris The surrounding areas of some of the acini were packed with pus, in a subacute inflammatory reaction, with infiltration by lymphocytes and polymorphonuclear leukocytes

Anatomic Diagnoses—The diagnosis was mild congestion of the brain and meninges, congestion of the liver with hepatomegaly, splenomegaly, infection with N americanus, subacute purulent prostatitis, malarial pigment in the spleen and liver, congestion of the renal glomeruli, and yellowish tinge to the internal organs (quinacrine ?)

In this case there developed, two days after termination of a course of quinacrine therapy for tertian malaria, a subacute toxic delirium with febrile temperatures, and the patient died thirteen days later, with hyperpyrexia The autopsy report is remarkable for the absence of significant observations The brain and meninges were moderately congested There were marked congestion of the liver, the spleen and the kidneys, subacute purulent prostatitis, and a yellowish tinge to the internal organs These observations rule out cerebral malaria, which could hardly be considered anyhow in a case of tertian malaria The remote possibility that death might have been due to the purulent prostatitis is ruled out by repeated sterile blood cultures and the absence of any observation at autopsy suggestive of septicemia Hence, the cause of death was toxic delirium, most probably due to quinacrine Still, we cannot account for the fact that the development in this case was so extremely serious except by assuming a specific hypersensitivity to quinacrine It is of interest to note that the patient in case 10 in our series, who received the large dose of 5 7 Gm of quinacrine hydrochloride, recovered from his psychosis after two and one-half days These observations certainly point toward considerable individual differences in tolerance toward the drug

Our observations agree fairly well with those of other authors No data were available in the literature regarding the time elapsed between the last attack of fever or the last positive blood smear, and the onset of psychosis The time elapsing between the last dose of quinacrine and the onset of psychosis varied in 17 cases observed by Kang and Jarvis,[16] Decherd,[9] Allen and co-workers,[11] Briercliffe[18]

and Kingsbury,[2] from no to eighteen days, with a median of 2 days The duration of the psychosis in 26 cases was observed by Kang and Jarvis,[16] Banerjee,[8b] Green,[4] Allen and co-workers,[11] Bispham[12] and Kingsbury[2] from one-half to thirty-seven days The average duration in 18 of these cases (in the rest of them the data were not given in all detail) was 4 4 days, the median, 2 days In all the cases reported in the literature, with the exception of 1 fatal case, the outcome was complete recovery No case of chronic psychosis following quinacrine therapy has been recorded The 1 fatal case was described by Decherd[9] The patient had received only 0 6 Gm of quinacrine hydrochloride and 0 06 Gm of pamaquine naphthoate in three days, when both drugs were discontinued and quinine was substituted, because of icterus and swelling of the liver Two days later the patient lapsed into delirium He became cyanotic, pulmonary edema developed, and he died on the second day of his psychosis Autopsy was not performed The impression prevails that in this case psychosis and death were due to acute damage to the liver However, the clinically observed swelling of the liver may have been due, as in our own case, to congestion only, and the apparent jaundice, to deposits of dye in the skin, as it occurs frequently in patients treated with quinacrine

ETIOLOGY AND PATHOGENESIS

That quinacrine was the direct cause of, and the most essential factor in, the psychoses in the cases observed by us and by other authors appears to be established by the following facts 1 The psychosis developed invariably a short time after a course of quinacrine treatment had been given 2 In almost all cases it subsided shortly after the administration of quinacrine had been discontinued, whereas it went on when the drug was still given after the mental symptoms had made their appearance (case 1) 3 The incidence of quinacrine psychosis, while rather low, is still by far higher than the incidence of toxic psychosis of unknown origin in the general population This rules out the possibility of mere coincidence 4 Cerebral malaria cannot be the cause of the mental disorder, (*a*) because the psychosis started in most cases after the patient had been cured of malaria and (*b*) because the incidence of the psychosis is not much lower with tertian than with estivoautumnal malaria, whereas cerebral involvement in cases of untreated tertian malaria is most uncommon 5 While it is true that many of our patients received quinine or pamaquine naphthoate in addition to quinacrine, no toxic psychoses were observed after the use of either of these drugs without quinacrine

Clark,[31] who was acquainted only with Kingsbury's[2] series, made the objection that the mental disorders may be due to malaria itself and raised the question whether the incidence of so-called quinacrine psychosis is not about the same as that of toxic psychosis from other causes in the general population These objections are dealt with under items

31 Clark, H C Recent Research on Prophylaxis and Treatment of Malaria, South M J **29** 752 (July) 1936

3 and 4 in the preceding paragraph Oden [32] mentioned a patient who came to the institution with a psychosis after quinacrine therapy, the condition cleared up, he left the institution and after some time came back with the same type of psychosis, though he had not been taking the drug Another patient, after being cured of so-called quinacrine psychosis, was given the drug again, but this time he exhibited no mental disorder These observations would tend to make one reconsider the etiologic importance of quinacrine if they had been substantiated by exact data on doses and on time which elapsed between the two psychoses or the two courses of quinacrine treatments, respectively Unfortunately, they were not

Granted, therefore, that the concept of quinacrine psychosis is justified, the question arises what factors determine the toxic effect, in a small number of cases, of a drug of comparatively low toxicity Probably, the dose is of no importance

In our series, the total doses of quinacrine hydrochloride given up to the outbreak of the psychosis varied considerably

Dose, Gm	No of Cases
0 5	1
0 9	1
1 1	1
1 5	2
1 6	1
1 7	1
1 8	3
1 9	2
2 0	1
2 2	1
2 4	1
3 0	1
5 7	1
Unknown	2

The patient in case 4, who received 3 Gm , died in delirium after thirteen days , the patient in case 10, who received 5 7 Gm , survived and recovered after two and a half days The average dose was 1 9 Gm , the median dose, 1 8 Gm The doses of quinacrine hydrochloride which were followed by a psychosis varied in the cases of Kang and Jarvis,[16] Banerjee,[8b] Bispham,[12] Decherd,[9] Lerro,[19] Green,[4] Briercliffe [18] and Kingsbury [2] from 0 6 to 2 1 Gm , with an average of 1 6 Gm in 22 cases The League of Nations' Commission on Malaria [33] (cited by Stitt [25]) reported that pyschoses have been observed especially in cases in which

32 Oden, J W , in discussion on Allen, Allen and Fulghum [11]

33 Fourth General Report of the Malaria Commission, Bull Health Organ, League of Nations **6** 895-1153, 1937

treatment with quinacrine was prolonged or the doses were large or excessive and in cases in which quinacrine mussonate was given by injection and followed by the oral use of quinacrine hydrochloride In some of our cases quinacrine had been given parenterally According to Brierclifle,[18] mental symptoms would appear toward the end of a five day period of oral administration of 0 3 Gm of quinacrine four times a day, whereas in case of intramuscular injection they would follow soon after the first injection or within twenty-four hours after the second injection With regard to the effect of parenteral administration of quinacrine, case 18 in our series deserves to be reported

Case 18—A Panamanian aged 25 was admitted to the hospital on Sept 8, 1943, with a history of headache, chills, anorexia and nausea for seven days preceding his admission He had never had malaria before The temperature on his admission was 100 6 F , otherwise physical examination showed essentially a normal condition The blood smear was positive for estivoautumnal malaria on the day of his admission The patient received 0 3 Gm of quinacrine hydrochloride by mouth On the following day his temperature rose to 104 F , and a few parasites were still found in his blood In the morning the patient was perfectly rational and not excited At 9 a m of this day he received 0 2 Gm of quinacrine hydrochloride intravenously At 10 30 a m he was found sitting in his bed, swinging his legs, rapping on the bed and conversing excitedly with other patients Shortly afterward he became violently hyperactive, threw a water jar and a medicine capsule on the floor and talked about getting out and buying meat and champagne When put in a wheel chair, he started throwing himself around and shouting at the top of his voice Sedation was effected with 3 grains (0 195 Gm) of sodium amytal and ¼ grain (1 6 mg) of morphine sulfate and he received large doses of thiamine hydrochloride and nicotinic acid His temperature was 105 6 F at 4 p m At that time the patient was semicomatose, and obviously under the influence of sedatives At 7 15 p m he was awake and talked rationally, though mentally somewhat sluggish His temperature dropped to 101 0 F at midnight and was normal the next day He remained mentally clear, with normal temperature Further smears were negative for the parasites, and the patient was discharged on Sept 16, 1943

In this case it appears that the sudden rise of the quinacrine level in the patient's blood produced by intravenous administration of 0 2 Gm of the drug, in addition to 0 3 Gm. given orally the day before, was an important factor responsible for the outbreak of an acute manic state, of only a few hours' duration

According to Allen and co-workers,[11] there seems to be a relation between the dose per kilogram of body weight and the duration of mental symptoms All 4 of their patients who took more than 25 mg per kilogram of body weight had symptoms of over ten days' duration, although 2 patients who had symptoms lasting more than ten days took only 19 1 and 24 1 mg per kilogram of body weight, respectively

These observations suggest a positive correlation between the dose of quinacrine and the development of mental disorder, but, obviously, this correlation is by far not high enough to account for the occurrence

of psychoses without any other contributing factor The large majority of patients in our series, as well as in other series, did not receive an overdose of quinacrine As to duration, we may refer to the patient in case 10, who received no less than 5 7 Gm of quinacrine hydrochloride and yet recovered from his psychosis after two and a half days

Another factor particularly stressed by Allen and co-workers [11] is the rate of elimination It is well known that quinacrine is eliminated (through urine and feces) very slowly According to Thonnard-Neumann and Ledoux,[34] quinacrine is eliminated within thirty-six days of the ingestion of the last dose Field and Niven [26] found quinacrine in the urine longer than four weeks "only in a few instances" On the other hand, Kehar [35] detected traces of quinacrine as late as sixty-five days after the final dose Allen and co-workers [11] called attention to the possibility that the normal accumulation of the drug may be increased, in certain cases, by deficient elimination and that this may account for the occurrence of toxic psychosis However, no clinical observations are available to substantiate this theory Damage to the kidneys or the liver (where quinacrine probably is accumulated) would have to be demonstrated as a complication in cases of quinacrine-treated malaria followed by psychosis We did not find any indications to this effect either in our own series or in the literature In the only case in which autopsy was performed (our case 4), nothing but congestion of the liver and kidneys was noted With experimental quinacrine poisoning, pronounced hyperemia and toxic central injection of the liver and fatty degeneration of the renal tubules were found, obviously a side effect of fatal poisoning in the animal experiment (Molitor [24])

In view of these observations, predispositional factors have to be considered That one of them may be the preexisting malaria seems to be supported (1) by the fact that the incidence of quinacrine psychosis in our series is significantly higher with estivoautumnal malaria than with tertian malaria, a difference which may be considered as due to the higher toxicity of Plasmodium falciparum and (2) by the fact that quinacrine psychoses or psychoses due to other acridine dyes have not been observed in other than malarial patients, though these drugs have been used in treatment of other diseases, such as quinacrine for giardiasis or acriflavine for gonorrhea However, it must be admitted that the total number of patients with conditions other than malaria treated

34 Thonnard-Neumann, E, and Ledoux, H A The Treatment of Malaria with Erion (Atebrin) Report of Seventy-One Cases, in Twentieth Annual Report of the Medical Department of the United Fruit Company, Boston, 1931, p 67

35 Kehar, N D The Influence of Food in the Stomach on the Absorption and Excretion of Atebrin, Rec Malaria Survey, India 5 405, 1935, Observations on the Absorption and Excretion of Atebrin, ibid 5 393, 1935

with quinacrine has been exceedingly small as compared with the number of malarial patients In addition, in 2 of our 19 patients no malaria parasites had been found in the blood, hence, the possibility exists that they did not have malaria at all

Racial predisposition has been claimed by some observers, inasmuch as natives in East Asia seemed to have psychoses after treatment with quinacrine far more frequently than Europeans (Stitt [25]) However, no racial prevalence could be demonstrated in our series (see also Beckman [30]) Kingsbury [2] stated the belief that mental predisposition is an important factor, and Govindaswami [17] found that certain types of mentally deranged persons, as well as alcoholic (see also Whittingham [36]) and arteriosclerotic patients, do not tolerate the drug well While our material does not actually confirm this assumption, it is quite probable that in psychopathic persons quinacrine psychosis is more prone to develop, just as are other forms of exogenic psychoses We may refer to a recent observation of ours not included in this series, that of an alcoholic patient who had his first attack of delirium tremens immediately after the intake of 0 6 Gm of quinacrine hydrochloride in two days, in treatment of mild estivoautumnal malaria The possibility that quinacrine medication may have touched off the alcoholic delirium in this case cannot be denied However, the clinical picture was that of delirium tremens, not of quinacrine psychosis

With all this the idea, vague as it may be, that there may exist an individual idiosyncrasy to quinacrine, as pointed out by Turner,[37] cannot be disregarded

There are two theories of the pathogenesis of the quinacrine psychosis, as pointed out by Kingsbury,[2] Molitor [24] and Banerjee [8b] 1 Quinacrine destroys trophozoites faster than quinine and therefore may liberate malaria toxins in large amounts Thus, this psychosis would actually be a malarial psychosis 2 The toxic effect on the brain may be due to the toxicity of quinacrine itself, similar to that of the scopolamine group of drugs or of the encephalitis virus

As to the first theory, Banerjee [8b] himself pointed out that all his cases were those of chronic malaria, in which cerebral stimulation is not known to occur In cases of malarial infection of low intensity or in cases in which the onset of the psychosis is delayed, this theory becomes hardly tenable It is possible, however, in view of the higher incidence of quinacrine psychosis in association with estivoautumnal malaria than with tertian malaria, that the infectious disease renders the brain susceptible to the toxic effect of quinacrine

36 Whittingham, H E, and Discussion on Experience with Synthetic Drugs in the Treatment of Malaria, Proc Roy Soc Med **32** 1085 (July) 1939

37 Turner, C C The Neurologic and Psychiatric Manifestations of Malaria, South M J **29** 578 (June) 1936

The second theory appears to be better supported In animal experiments Hecht [38] noted evidence of cerebral stimulation following lethal doses According to Molitor,[24] quinacrine is only occasionally found in the cerebrospinal fluid, but it appears in the brain after injection of lethal doses In the animal experiment toxic doses cause clonic convulsions As previously mentioned, epileptiform seizures have also been observed clinically after injections of quinacrine Of particular interest from the therapeutic point of view, to be discussed later, are experimental observations by Manifold,[39] who studied various acridine dyes for their relative toxicity to carbohydrate and pyruvate oxidation systems of brain tissue in the test tube Among them, acriflavine was found to be highly toxic, even at very low concentrations, and other acridine dyes still toxic, though to a lesser extent Apparently, quinacrine has not been tested with this method, however, being closely related to the other members of the acridine dye group, it might very well have the same form of toxicity, which consists in an inhibition of oxidative processes in the brain This mechanism is essentially the same as that found to be active in cases of vitamin B deficiency, a fact which would account for the similarity of psychiatric pictures of quinacrine and deficiency psychoses

As to treatment, we found valuable high doses of concentrated vitamin B complex, particularly thiamine hydrochloride and nicotinic acid, not only because there is a sound theoretic basis for it (Manifold [39]) but because we observed dramatic results at least in 2 of our cases (15 and 16), in which the psychosis had been going on for five and six days, respectively, and cleared up one to two days after the administration of vitamin B preparations While it is true that most patients recover spontaneously from the psychosis, treatment does not appear unnecessary in view of the fact that occasionally quinacrine psychosis may last several weeks

Our use of vitamins followed the routine for treatment of alcoholic psychosis

Thiamine hydrochloride, 50 mg intravenously, four times a day
Thiamine hydrochloride tablets, 10 mg, three times a day
Nicotinic acid, 50 mg, three times a day
Vitamin B complex capsules,[39a] 2, three times a day

In addition, fluids should be forced, in order to speed up elimination of the drug For the same reason, the bowels should be kept open, both during and after the treatment

38 Hecht, G Pharmakologisches uber Atebrin, Arch f exper Path u Pharmakol **170** 328, 1933

39 Manifold, M C The Effect of Certain Antiseptics on the Respiration of Brain Tissues in Vitro, Brit J Exper Path **22** 111 (June) 1941

39a Each capsule contained 5 mg of thiamine hydrochloride, 25 mg of riboflavin and 25 mg of nicotinamide

SUMMARY

A series of 19 cases of toxic psychosis following quinacrine treatment of malaria, as observed in Gorgas Hospital from 1935 to 1943, is reported

The incidence of quinacrine psychosis in Gorgas Hospital was 0.39 per cent of all quinacrine-treated patients, or about 1 out of 250 so treated. It appeared to be moderately higher with estivoautumnal than with tertian malaria.

The clinical characteristics of our observations are described and compared with those in 43 cases previously published by other observers. Case histories and postmortem observations are given in 1 fatal case of quinacrine psychosis and in 1 case of quinacrine psychosis superimposed on early dementia paralytica.

The etiologic factor responsible for quinacrine psychosis is probably to be found either in an individual hypersensitivity to the drug or, in some cases, in constitutional psychopathy. Toxic damage to the central nervous system caused by malaria seems to be a contributing factor. The effect of overdosage of the drug remains doubtful. The pathogenesis of quinacrine psychosis is probably determined by hypersensitivity to the drug and its specific toxic effect on brain tissue previously sensitized by malarial infection.

Prevention of quinacrine psychosis consists in recognizing that a certain few persons are probably hypersensitive to the drug. The dosage should rarely exceed 2.8 Gm. in one course of treatment, especially when the therapeutic effect can be attained with a lower dose. Parenteral, in particular intravenous, administration should be limited to cases in which therapeutic results cannot be obtained otherwise. For treatment, high doses of vitamin B preparations and forced intake of fluids are recommended. The prognosis is favorable, with few exceptions. No chronic mental ailment has been observed to develop from this condition.

PREVENTION AND TREATMENT

Quinacrine has proved, for the last ten years, to be such a valuable addition to medical resources in combating malaria that possible complications arising during treatment, even if they were somewhat more frequent than they actually are, would not justify its abandonment. An incidence of 1 in 250 treated patients, such as that of quinacrine psychosis, is certainly not serious, the more so as the mental disorder is usually of short duration, ending in recovery. Still, it deserves attention, and whatever may be possible to reduce it should be done. In the first place, the dosage and timing of quinacrine treatment must be considered. We have hardly any positive evidence to prove that overdosage per se is an essential factor responsible for the development

of quinacrine psychoses, considering the fact that in the large majority of cases in the literature, as well as in our series, the amounts of quinacrine given were very moderate However, taking it for granted that a small number of persons appear to be hypersensitive to this drug, and that these hypersensitive patients are more likely to respond with psychotic symptoms to higher than to lower doses, we suggest moderate conservatism with respect to dosage and timing of quinacrine treatment The amount of 2 8 Gm given in one week, as recommended by the War Department, Circular Letter no 153,[10] ought to be considered as the upper limit Experience shows that a dose of 2 Gm, or even less, is usually sufficient for successful treatment of the clinical attack As it seems that parenteral methods of treatment are more likely to bring on psychoses than oral ones, they ought to be used only when the seriousness of the case requires it These precautions as to dosage, form of medication and timing ought to be considered carefully, particularly in cases in which the history gives evidence of psychopathy or chronic alcoholism

40 The Drug Treatment of Malaria, Suppressive and Clinical, United States War Department, Circular Letter no 15, Washington, D C, Government Printing Office, August 1943

NYSTAGMOID MOVEMENTS AND VISUAL PERCEPTION

Their Interrelation in Monocular Diplopia

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IN A previous communication one of us (M B B) reported 4 cases of monocular diplopia and polyopia in patients with disease of the brain [1] Although each case presented a different clinical and pathologic problem, there were certain features which all had in common The double or multiple vision was most pronounced on prolonged or close fixation Two of the patients, who were studied in detail during the period when the illusions were manifest, complained of multiple image formation only after prolonged fixation on an object Furthermore, the diplopia and polyopia seemed to be confined to the macular field of vision Since the act of close fixation is usually associated with an increase in ocular movements, it was felt that the latter might in some way be related to the phenomenon of monocular diplopia and polyopia Kubie and Beckmann [2] found that increased ocular movements resulted in diplopia (presumably binocular and without palsies of extraocular muscles) in patients with lesions of the optic chiasm In other words, an alteration in the oculomotor status (increased ocular movements) is associated with a change in visual perception (multiple images). Theoretically, a decrease in movements of the eyes should also be associated with a change in visual perception

In order to test these hypotheses, 2 cases were studied In the first case, that of a patient with encephalitis, various methods were employed to assess the degree of increase in ocular movements which occurred during fixation and during the appearance of monocular diplopia In the second case special tests of visual perception were carried out after the ocular movements (congenital nystagmus) had been temporarily

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1 Bender, M B Monocular Diplopia and Polyopia of Cerebral Origin, Arch Neurol & Psychiat **54** 323-338 (Nov-Dec) 1945

2 Kubie, L S, and Beckmann, J W Diplopia Without Extra-Ocular Palsies, Caused by Heteronymous Defects in Visual Fields Associated with Defective Macular Vision, Brain **52** 317-333, 1929

abolished by the injection of sodium amytal [3] The relationship between ocular unrest and formation of multiple images could thus be investigated in two ways (1) by direct observation of the movements of the eyes which occur during an existing diplopia, and (2) through induction of monocular diplopia (by altering the subject's ocular movements with a drug)

METHOD

It has long been known that ocular movements are present during fixation in normal subjects These movements can easily be demonstrated with the help of the standard laboratory methods (Dodge [4], Judd and associates [5]) According to the measurements of Adler and Fliegelman,[6] the movements represent a fine tremor rather than excursions of a nystagmoid character Their extent is well below 1 degree In cases of monocular diplopia it is assumed that instability of ocular movements during periods of fixation leads to somewhat wider excursions

These relatively extensive movements should then become manifest even without the use of complicated apparatus Many of the early investigations on movements of the eyes were carried out in a simple clinical setting Such observations, even if not exact, may be sufficiently suggestive to make a preliminary test of certain hypotheses possible Among these older methods there are at least three which are promising in a clinical situation (1) the so-called peephole method, (2) the mirror method and (3) the after-image method The first two procedures enable the experimenter to observe directly any gross ocular movements in a subject The third method is unique in that the subject himself observes and describes the movements of his eyes during the act of viewing an object It requires of the subject a particular degree of cooperativeness and intelligence But given these conditions, it is definitely superior to the first two approaches It was used extensively by von Helmholtz [7]

1 The peephole method (Miles [8]) consists in observing the subject's eye through a small hole in a paper he is reading or a picture he is

3 Bender, M B Effects of Barbiturates on Ocular Movements (Nystagmus), to be published

4 Dodge, R An Experimental Study of Visual Fixation, Psychol Monogr **35** 1-95, 1907

5 Judd, C H , McAllister, C N , and Steele, W M Introduction to a Series of Studies of Eye Movements by Means of Kinetoscopic Photographs, Psychol Monogr **29** 1-16, 1905

6 Adler, F H , and Fliegelman, M Influence of Fixation on the Visual Acuity, Arch Ophth **12** 475-483 (Oct) 1934

7 von Helmholtz, H Handbuch der physiologischen Optik, Leipzig, L Voss, 1866

8 Miles, W R The Peep-Hole Method for Observing Eye Movements in Reading, J Gen Psychol **1** 373-374, 1928

scanning The experimenter is seated behind the paper, and partly concealed by it, with his face turned toward the subject

2 The mirror method is more frequently used in ophthalmologic and neurologic examinations A plane mirror is placed beside the object which is being inspected, and the experimenter watches the subject's ocular movements in the mirror

3 The after-image method consists in giving the subject a small, distinct after-image for the eye which is to be observed The subject then views the test object, as long as the after-image persists, its excursions over and around the test object define the subject's ocular movements to the subject himself provided these movements are not too rapid

OBSERVATIONS

All three methods for direct observation of ocular movements were used in our first case The patient, a seaman first class, aged 21, had been studied over a period of four months after his attack of acute encephalitis following measles, which had led initially to a parkinsonian state As the paralysis agitans subsided, only a few disturbances remained, primarily centered around the patient's vision

Prior to his induction into the United States Navy the patient had studied chemistry and had won high academic honors He always had a vivid after-imagery and had made spontaneous observations on these phenomena To the patient's distress, this after-imagery was completely lost after the acute stage of his disease, and only two months later did it gradually return

During his period of recovery the after-images deviated from the normal in the same measure as did the patient's visual functions in general After an initial phase bordering on visual agnosia had been overcome, the patient's visual organization was characterized by an extreme amount of fluctuation and obscuration The specific perceptual disturbances can perhaps be subsumed most adequately under the concept of a loss in perceptual constancies, particularly constancy of size When objects were exhibited to the patient and then gradually moved away from him, their apparent size decreased much more rapidly than the usual constancy effect would allow At the same time, the patient's after-imagery (when he regained it) did not follow Emmert's law, that is, the images did not change in apparent size when projected against backgrounds of varying distance [9]

However, the most outstanding abnormality was the patient's monocular diplopia, already described [1] The patient had a congenital convergent strabismus of the left eye, and vision in this eye had always been poor (amblyopia ex anopsia) He had never experienced any diplopia His visual fields were intact Yet, two and a half months after his acute illness, monocular diplopia developed in the patient's better, or apparently normal, eye (right eye), although it was also found, but less constantly, in the left eye The double image was always incomplete, displaced to the left and slightly below the original When the test object was moved away from the patient, the distance between the double image

9 The connection between the phenomena summarized by Emmert's law and the effects of size constancy has been formulated by Boring (Am J Psychol 53 293-295, 1940)

and the original image showed a slight increase, and the double image became less complete Even at that time the patient stated occasionally that he could see a faint after-image and the double image of an object simultaneously

Throughout his period of recovery our patient observed the gradual change in his condition and gave detailed oral and written reports There were no indications of a magnification or a minimization of symptoms When he submitted to the experiments which are described in the next paragraph, his after-imagery had almost completely returned, while his monocular diplopia still persisted For this reason, although all three methods of observation of ocular movements were employed, special emphasis was placed on the third, the after-image, method (The patient's left eye was covered throughout the experimental sessions)

Peephole Method—During maintained fixation this method was not sufficiently adequate to permit conclusive observations, regardless of whether the patient reported single or double vision

When he read a newspaper article (held at 12 inches [30 cm] from the eyes, the lines being 2 inches long [5 cm] and ⅛ inch [32 cm] apart, the patient's eye gave the impression of sluggish and somewhat excessive saccadic movements, superimposed on continual horizontal nystagmoid movements This nystagmus was so fine that it was impossible for the observer to decide whether the nystagmus was of equal extent to the right and to the left

Mirror Method—1 Fixation As long as the patient reported single vision, his eye appeared fairly steady After from two to five seconds there was a slight, but brisk, shift of the right eye to the patient's right Then the fine lateral nystagmus was noted At the same time the patient announced the appearance of a double image

2 Reading Observations through mirrors revealed the rather sluggish saccadic movements of the eye from left to right The fine lateral nystagmus was only occasionally noticeable If the left eye was temporarily uncovered, it could be seen that it frequently "lagged" behind the right

After-Image Method—The patient's ocular movements during fixation were observed by the patient himself by means of the after-image of a small, luminous disk supplied by the ophthalmoscope Preceding each trial, the patient's eye was stimulated by shining the beam of the lit ophthalmoscope into the right eye After the initial trials, the patient held the ophthalmoscope himself, since ocular movements during stimulation were minimized in this way However, regardless of any movements of the eyes which might have occurred during stimulation, a distinct disk-shaped after-image was obtained with periods of exposure as long as forty-five seconds Immediately after stimulation, the patient was asked to fix the center of a red cross on white paper, 12 inches from his right eye The arms of the cross measured 1 inch (2 54 cm) each The patient was urged to fixate as steadily as possible (with his chin locked in his hands to minimize head movements) He was told to report the relative position of the after-image to the center of the cross, as well as any shifts in the position of the after-image For obvious reasons, he was kept unaware of the fact that these excursions of the after-image were indications of his ocular movements The patient was further instructed to report immediately the appearance of the double image of the cross—whether it appeared instantly or after a lag—and to observe the shifts, if any, in the position of the double image relative to the center of the cross (These detailed instructions were given the patient gradually during the first three trials At first he was asked only to fix the center of the cross

and to report all movements of the after-image) After a short period of practice, the patient seemed to have little difficulty in reporting on both after-image and double image in relation to his point of fixation This may be due to the fact that both remained within or close to foveal vision—indeed, everything took place within a range corresponding to an angular distance of slightly less than 8 degrees

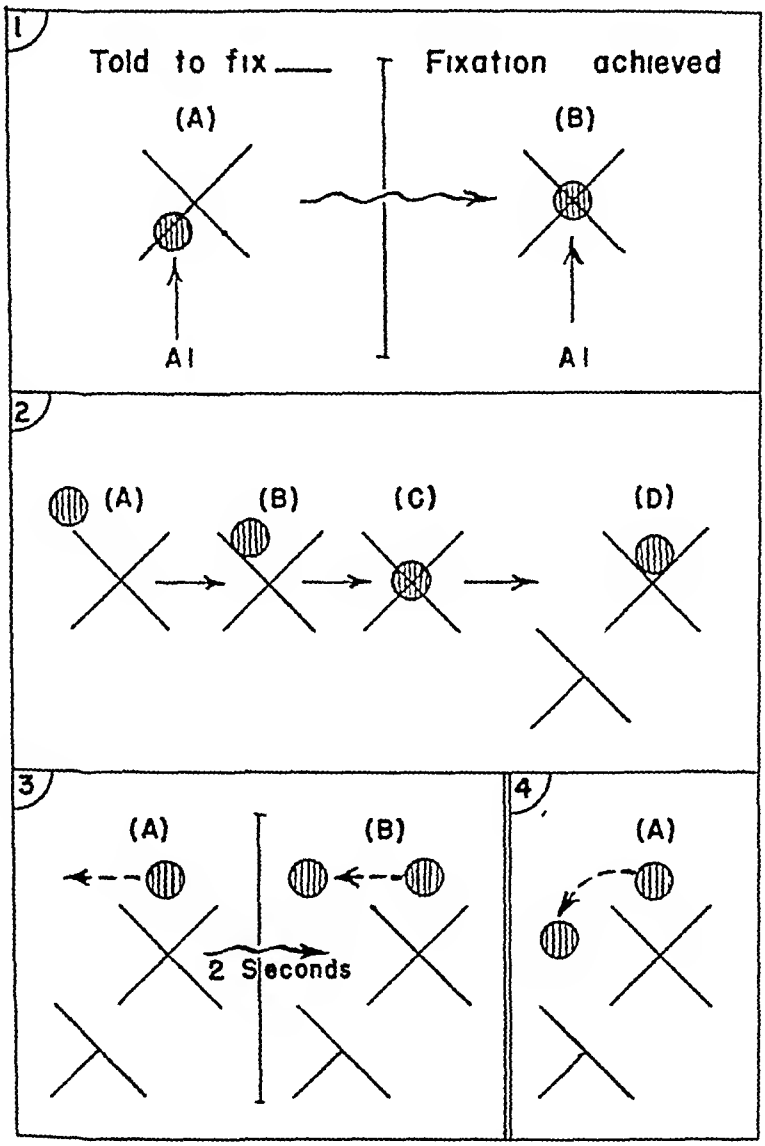

Fig 1—*1 to 4* patient's after-images (represented by disks) in relation to the cross (*1, A*) The patient is instructed to fix the center of the cross, (*B*) fixation is achieved, the after-image has moved into the center of the cross (*2 A*) The patient is again attempting to fix, the after-image moves through *B* and *C* into the center As soon as the center has been reached, the double image appears (*D*) (*3* and *4*) Periodic excursions of the after-image occur to the left, the after-image traverses a distance equal to that between the original and the double image, then it is seen "suddenly" back in the center, or slightly above the cross

First Trial The patient observed how his after-image moved into the center of the cross, i e, the initial adjustment of fixation At the same time, the early phases of flight of colors in the after-image were reported (fig 1*1*)

Second Trial (fig 12) Although the patient was instructed to attend only to the after-image, its movements and changes in color, he spontaneously announced the appearance of a double image It was incomplete, as usual for this patient, and appeared to the lower left of the original cross, ¾ inch (1 9 cm) away from it in the patient's estimation (This corresponds to an angle of about 4 degrees) From the illustration it will appear that the double image was reported only after fixation had been achieved, that is, as soon as the after-image had come to a first (temporary) rest in the center of the cross

When asked specifically whether he thought this double image had been there "right away" or whether it appeared only at the time he announced it, our patient could not reply with certainty He thought that the double image was instantly there, as soon as he looked at the cross However, he was not sure whether this was true in all trials On the other hand, he was definite in his statement that the double image did not move at all, whereas the after-image moved "almost constantly" The after-image came in "from above and from the left," down toward the center of the cross Then, the patient said, the after-image was "suddenly" off center again (usually above) and moved back on or near the center Then this cycle recurred, repeating itself about half a dozen times, until the after-image faded out

Third Trial The same results were obtained as on the previous trial Again, the patient reported a double image after he had stated that the after-image had "reached" the center of the cross, but he was not certain about time relationships Since the patient had to report verbally on all these movements while the movements were still going on, nothing but a rough estimate of the time element could be obtained (fig 12)

Fourth Trial The patient saw his after-image immediately, above the center of the cross and to the left By the time it moved into the center of the cross, and not before, the double image became visible to the lower left

Fifth Trial The after-image was immediately in the center of the cross, the double image was announced as appearing instantly, and it did not move (The patient had been asked to pay special attention to whether the double image moved with the after-image, in a different way or not at all) Within "less than a second" the after-image was seen on top of the cross (fig 13), and then it moved to the left A second later the after-image was reported at the same height as the double image, that is, above the double image but at the same distance from the vertical line drawn through the center of the cross, whereas the double image remained stationary (fig 13)

Sixth Trial The after-image appeared to move first to the left in a slight downward curve, but, again, it came to a stop at the same height as did the double image (fig 14) After the first reported excursion of the after-image in this trial, the patient specified six more excursions (in retrospect) for the next two and a half seconds The after-image now moved steadily, but swiftly, along a horizontal (linear) path to the left, "always stopping when it got into the same vertical line with the double image" (same as fig 13) The double image remained stationary throughout As one would expect, the patient did not know when and how his after-image got back in or near the center of the cross after each horizontal excursion

Throughout these experiments, the widest excursions of the after-image corresponded to an angular distance of 8 degrees Assuming 2 degrees as the maximum diameter of the fovea centralis, it is to be noted that the nystagmoid movements during fixation carried the image periodically into the pericentral area Varying values have been given for the "fixation tremor" in normal

subjects, but Adler and Fliegelman's measurements[6] showed them to be about 25 minutes, and Duke-Elder's[11] review of the experimental literature on the subject gives 4 minutes as the average Our patient's change in ocular position thus must have been much greater than that observed in normal subjects

In spite of this, the patient was neither directly nor indirectly aware of these movements The weak after-image moved with his eye, describing, as in normal subjects, the full amount of ocular movement Conversely, the continual retinal displacements of the stimulus object (due to the unrest during fixation) were perceived by the patient not as oscillation of one object, but as a stationary double configuration The only motion perceived was that of the after-image, and therefore the latter actually defined the full amount of ocular movements as projected into space These relationships could easily be demonstrated As soon as the situation was changed by making the patient conscious of his ocular movements, the double image disappeared The patient was instructed to shift his eye and try to make the double image move on its background in the same manner as the after-image had been reported to move The result was an immediate disappearance of the double image, while the after-image remained visible, although moving in erratic fashion, since the patient had become aware of gross movement of his eyes and the "unconscious" nystagmoid movements had been stopped, or at least modified

Comment—The observations on this patient demonstrated (*a*) an increased fixation tremor and (*b*) a concomitant appearance of monocular diplopia The diplopia set in as soon as the nystagmoid movements began The slow phase was always in the direction of the double image, and the distance between the two images was equal to the angular distance described by the excursions Finally, in comparison with the ocular unrest during fixation in normal subjects, the patient's fixation tremor was definitely increased, although it did not reach the extent of a regular nystagmus[12]

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10 Footnote deleted by author

11 Duke-Elder, W S Text-Book of Ophthalmology, St Louis, C V Mosby Company, 1938, vol 1, pp xxxi and 1137

12 This fixation tremor might help to explain the incompleteness of the double image One could argue that a greater extent of excursions would have led to the formation of two complete double images, and an even greater extent to the appearance of polyopic phenomena However, one does not know enough about the corresponding cortical processes Closely adjacent retinal images are probably represented on the striate cortex by closely adjacent excitation processes, even though this representation exists only in a dynamic sense The occurrence of mutual attraction and interference (on the cortical level) between such closely adjacent percepts has been shown by Werner (Am J Psychol **53** 418-423, 1940), who demonstrated these effects by means of a rapidly alternating separate presentation to each eye Under pathologic conditions, rivalry can be demonstrated even for a single eye (as a rivalry between the two half-fields) The incompleteness of the double image would thus appear as an incomplete fusion, which might well be what Goldstein[14] meant by assuming abnormal "diffusion" on the visual cortex In this connection, it should be noted that the threshold for flicker and fusion were notably reduced for this patient, while he showed an augmentation in his contrast phenomena, particularly internal contrast

It will be recalled that the patient had a congenital convergent squint Although this condition did not lead to binocular diplopia until after his encephalitis, it is conceivable that it supplied a latent disposition for a specific form of diplopia and concomitant ocular unrest [13] The excursions of his right eye during fixation were primarily to the left, and the double image was consistently referred to the left, or, in other words, to the patient's weak side

The nystagmoid movements to the left were increased whenever objects under fixation were moved farther away from the patient, and thereby decreased in size on the retina Strong contrast—internal and external contrast—likewise made steady fixation more difficult for the patient Fixation is primarily a function of the occipital lobe, and it is not unlikely that both the diplopia and the unsteadiness of the eyes during fixation were results of one and the same disturbance in function of the occipital lobe A generalized disturbance in visual functioning on this highest level had been found for this patient in other respects, as, for instance, in the impairment of size constancy

Generalized disturbances in perception were postulated by Goldstein [14] in his own cases of monocular diplopia In keeping with his "field theory" of cortical function, he assumed that injured or diseased cortex is characterized by an abnormal "diffusion" of figural processes If this spread of the configuration over its background becomes extensive enough to involve areas with different space values, the formation of double or multiple images, will result Our own direct observations on the role of ocular movements in the appearance of monocular diplopia do not detract from such a diffusion theory, nor do they contribute to its confirmation

In point of fact, our observations show only a concomitance of irregular movements of the eyes with the occurrence of monocular

13 Bielschowsky's *locus classicus* (Arch f Ophth **44** 143, 1898) on monocular diplopia associated with strabismus does not consider the role played by ocular movements Cass (Brit J Ophth **25** 565, 1941) found that he was able to induce monocular diplopia in cases of congenital squint by a method of flicker This procedure, he asserted, stimulated the true and the false macula in rapid succession and thus produced diplopia in the squinted eye Similar to this artificial situation is the spontaneous monocular diplopia, which has been observed at times in hemianoptic persons during the emergence of a pseudofovea, when retinal correspondence was in the process of restructuring itself In our own cases of monocular diplopia, the emergence or existence of a permanent pseudofovea did not seem to be a necessary condition However, the increased ocular movements during fixation in our patients carried the image periodically over regions of different excitability

14 Goldstein, K. Ueber monokulare Doppelbilder Ihre Entstehung und Bedeutung fur die Theorie von der Funktion des Nervensystems, Jahrb f Psychiat **51** 16-38, 1934

diplopia One is tempted to say that the ocular movements are the "cause" of the diplopia, but it could just as well be argued that the diplopia occurs and that the patient therefore begins instantly to shift his eyes involuntarily back and forth between the true and the "false" image In the light of our observations in this, and in the following, case, we think, rather, of the two phenomena as simultaneous The disturbances in movement and in perception are only two aspects of the same disruption in function, just as normal perception depends on normal motion and vice versa

CASE 2—While in case 1 monocular diplopia developed after an acute infectious process, in our second case, that of a patient with congenital nystagmus, monocular diplopia developed under artificial conditions

The patient, a 23 year old Marine, was admitted to the hospital because of dizziness and a sense of weakness The general physical and neurologic examinations revealed nothing of significance except for nystagmus The nystagmus was pronounced enough to arouse the attention even of the casual onlooker On examination it was found to be spontaneous, continual, irregular and almost exclusively in the horizontal plane Occasionally, a slight rotatory component (clockwise) could be noted The horizontal excursions of the eyes were more pronounced to the right than to the left However, the difference was too small to be noted on direct observation, it was found by use of the slit lamp It was further noted that the nystagmoid movements of the right eye were less pronounced than those of the left, that is, they covered less distance and were correspondingly slower than those of the left eye But since the excursions were strictly synchronous, the difference between the two eyes became noticeable only on observation through the telescope

In both extreme lateral positions the nystagmus was definitely less pronounced than on forward gaze This was more noticeable when the patient looked to the right For this reason, the patient had acquired a habit of inspecting objects "out of the corner of his eyes" Whenever he wanted to see finer details of objects, he brought his eyes into the right extreme lateral position He complained about this "bad habit" and said that when he was following movies on the screen his head was "pulled" to the left and his eyes were shifted to the right, where he could see better [15]

Actually, it could be shown that his acuity in binocular vision and straight forward gaze on the Snellen chart was inferior (6/20 in each eye) to the acuity in the extreme lateral position (10/20 in each eye), in which the nystagmoid movements were minimized The lens system itself appeared intact, as were the external ocular muscles There were no defects in the visual fields

However, the patient followed this "pull" only under special circumstances, e g, during prolonged fixation or while attempting to recognize persons at a distance It was definitely not an abnormal tonic pull to either side There were no symptoms of cerebellar or labyrinthine involvement. Efficiency in the left extreme lateral position was equal to the one in the right After repeated Barany turning tests, the patient experienced vertigo but showed only his usual nystagmus on

15 In another case of (presumably) congenital nystagmus analogous behavior was found In that instance the nystagmus was primarily upward and downward, and the patient had "learned" to minimize this nystagmus, and hence to improve his vision, by rolling both eyes slightly upward during prolonged fixation

forward gaze, without increase in excursions or change in pattern Nystagmus in the extreme lateral position was increased However, there was little, if any, past pointing

Induced Opticomotor Nystagmus—On stimulation with a rotating striped drum the patient did not show any opticokinetic nystagmus, regardless of the direction in which the stripes were moving However, thresholds for flicker and fusion were greatly reduced when the stripes moved at right angles to the patient's horizontal nystagmus

Status of Patient's Visual Perceptions Before Experiment—In spite of the extreme irregular spontaneous movements of his eyes, this patient had achieved a surprisingly adequate visual performance [16] He had never had any diplopia "Blurring" occurred occasionally while reading, and he stated that "the lines became all one black bar" A single light in the dark would appear as a "neon sign" (oriented horizontally, like his nystagmus), especially if the patient himself were moving

After-images were difficult to obtain A drawing of the American flag in complementary colors was seen as a light, colorless field, without detail, shrinking and expanding at a rapidly fluctuating rate Stimulation with a strong disk of light (100 watt bulb held at 1 inch from the eyeball for five seconds) resulted in the perception of a horizontal luminous bar (also described as a "neon sign" by the patient), again growing longer and shorter There was also a rapid alternation in colors (blue, green, blue, green, etc) which was synchronous with the changes in the length of the after-image

Except for horizontal elongation of the after-image and of single points of light in a dark field, the patient did not show any distortion effects in his visual perceptions A heavy black *L* on a white card remained equilateral and unchanged on prolonged fixation, in spite of changes in position A fine dark line on a white ground never appeared double, although when it was held in the vertical position the patient complained that he saw dark streaks, "shadowy," parallel to each other and shooting horizontally across the vertical line

Reversible figures, such as the Schroder staircase and the double face, were seen at normal rates of alternation

However, in judging lengths of lines at varying distances, the patient showed an increasing tendency to underestimate length with increase in distance. The difficulty was more noticeable with horizontal than with vertical lines His performance was suggestive of an abnormally low degree of size constancy, particularly in the horizontal meridian

After this cursory inventory of the patient's visual functioning, the impression was gained that for all practical purposes his nystagmus had to be considered as congenital [17] This explains the amount of adaptation achieved On superficial examination at least, the continuous horizontal deviations of the patient's eyes seemed barely to affect the appearance which his world had for him Under these conditions, the question presented itself What would happen to his visual organization if this nystagmus could be arrested at least temporarily, as with the use of barbiturates? Barbiturates have been found to abolish various forms of nystagmus,

16 By contrast, in patients whose nystagmus appears when one eye is closed or binocular vision is interrupted (latent nystagmus), vision becomes much impaired and objects appear to jump

17 The clinical history showed that during the first years in school the patient was repeatedly sent to the family doctor and ophthalmologist because of this nystagmus

especially the congenital form[4] This abolition is temporary, lasting from two to three hours

Experimental Arrest of Patient's Nystagmus—The patient was given an injection of 0 3 Gm of sodium amytal by vein, and the following observations were made

Three Minutes Most of the spontaneous horizontal nystagmus evident on direct gaze disappeared, and there were coarse, slow nystagmoid movements only when the eyes were turned in extreme lateral position

Nine Minutes There was no nystagmus on convergence, fixation, upward gaze or downward gaze, but there was pronounced nystagmus in the extreme lateral position The status preceding the injection was thus completely reversed The generalized effects of the barbiturate were noticeable but not pronounced The patient felt "high," or "punch drunk," and asked whether he would have a hangover

Fourteen Minutes He stated, "I hardly feel my eyes from all that shot"

Seventeen Minutes The nystagmus in the extreme lateral position became less pronounced

Twenty-One Minutes A slight, oscillatory tremor of both eyes reappeared on forward gaze From then on, for eighty minutes, this nystagmus continued to fluctuate in extent, increasing and decreasing at five to ten minute intervals but becoming more pronounced each time The nystagmus in the extreme lateral position showed a concomitant decrease

Twenty-Nine Minutes The patient said, "My eyes feel better than before the shot Are the movements coming back?" (He showed some nystagmus on forward gaze at this point)

Thirty-Eight Minutes The patient rubbed his eyes vigorously, frequently blinking, and complained that his eyes hurt badly "It's getting foggy again—things look like before the shot" (conspicuous nystagmus)

Forty-One Minutes He said "I could see better after that shot—now it comes back"

Forty-Three Minutes Full nystagmus was present on forward gaze, for the first time since the injection

Disturbances in Visual Perceptions During Period of Reappearance of the Nystagmus—Forty-three minutes after the initial injection, when the full nystagmus had returned for the first time, the patient looked at a pencil held at arm's length before him He said it was getting "wider" He also stated that the doctor's face was "broad—like a fat man's"

Special examinations revealed the following disturbances

1 *Perception of Single Vertical Lines* A straight vertical line drawn with a pen on white paper at 2 feet (60 cm) from the patient elicited this comment, "It's thick and stays thick—a half-inch at least" A heavy black line (about ⅜ inch [96 cm] thick), printed on white cardboard, was exhibited in vertical orientation, 2 feet from the patient The patient insisted that this line, too, was ½ inch (12 7 mm) thick A minute later he exclaimed, "Now the line is getting thinner all the time"

2 *Single Lines, Rotated into Horizontal Positions* The printed line was again shown to the patient, in the same vertical position, a minute and forty seconds after it seemed to the patient to get thinner and thinner The patient said again that it appeared to be ½ inch thick At this point the card was rotated through 90 degrees, until the heavy black line came into horizontal position The patient reported that the line had become thin, but "it's about a yard long" With the same card in a slanted position (45 degrees above the horizontal), the patient drew a trapezoid

thickest on its upper end (fig 2 *A*) Instructed to shift his fixation to the lower end of the line, he reported that the trapezoid had become thickest at its lower end (fig 2 *B*)

3 Two Lines Two lines of equal length at right angles to each other, forming an L, were seen by the patient as distinctly unequal, the vertical line being short and thick, the horizontal line thin and long (patient's drawing, fig 2 *C*)

4 Closed Figures A heavy black circle printed on a white card (thickness of periphery, 3/8 inch) looked to the patient "like a football," that is, broadened in the horizontal dimension (patient's drawing, fig 2 *D*) A triangle appeared distorted in a similar, though less symmetric, fashion, indicating a greater amount of distortion (elongation) to the right (patient's drawing, fig 2 *E*) [18]

5 After-Images Only an incomplete, light after-field, without detail and color, was obtained after repeated exposure of an American flag, drawn in the complementary colors The patient complained that he could not maintain fixation

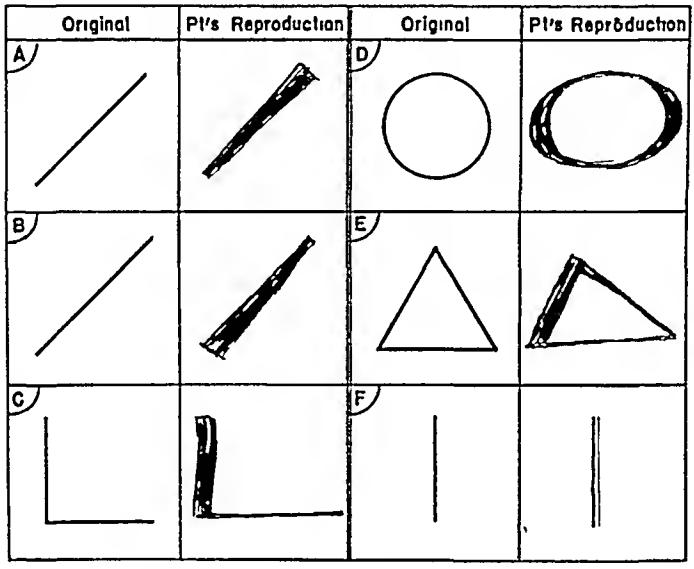

Fig 2—Distortions of perceptions during the period of recovery from sodium amytal (patient's own drawings) The patient was fully aware of these distortions *A*, fixation on upper (right) end of line, *B*, fixation on lower (left) end of line

during exposure The lines of stars would "run together" and black out—"just like one of these reading blurs," of which he had complained before the experiment After prolonged fixation the whole flag "blacked out" at five second intervals, and the patient felt compelled to look away

6 Reversible Figures While the after-imagery was not improved over the preexperimental status, the patient showed an increased flexibility in obtaining the Schroder staircase effect The first reversal was reported almost immediately, with rapid shifts following in cycles of three to five seconds With signs of excitement, which increased his usual difficulties in verbalizing what he saw, the patient

18 All these perceptual disturbances are clearly related to the patient's horizontal nystagmus In 1 instance (the triangle fig 2 *E*) we even found a greater distortion to the right, in keeping with the fact that the greater excursions of the patient's eyes were to the right during nystagmus

attempted to describe a peculiar effect The "bottom line" of the staircase appeared lengthened and shortened in comcomitance with the shifts in perspective It appeared long when the figure was seen right side up and short when it appeared upside down

7 Monocular Diplopia Ninety minutes after the injection of the first cubic centimeter of sodium amytal, the patient was again confronted with a straight vertical line drawn with pen on white paper No "broadening" of the line was reported After ten seconds the line was slowly rotated about 45 degrees out of the verticle toward the patient's left The patient reported that another line, fainter than the first one, "jumped out" to the left of the original The two lines were described as close together and "quivering" They were seen binocularly and monocularly with each eye Their appearance and relative distance remained unchanged in binocular and in monocular vision It was also noted that changes in distance of the stimulus from the patient's eyes did not induce changes in relative distance of the original image and the double image But the diplopia in itself was evanescent Beyond the range of 2½ feet (76 cm) it could not be obtained When the original line was rotated out of the vertical, there were no changes Both lines stayed parallel, "about 0 5 mm apart," and remained in this orientation even after the horizontal had been reached The line appeared still distinctly double, with the fainter, double, image below the original image (patient's drawing, fig 2 *F*) However, after he had maintained fixation (at a distance of 16 inches [40 cm]) for fifteen seconds with the original line in its horizontal position, the images grew "fuzzy" and became single

The experiments were terminated one hundred minutes after the injection At that time the patient was relaxed, and his nystagmus had again decreased considerably Apparently, the fluctuations in oculomotor function, which had been in evidence throughout the period of recovery from the effects of the drug, were still persisting Casual examination showed absence of diplopia and a recurrence in the "thickening" of vertical lines

Comment—These observations clearly indicate that the patient's changes in visual perception were more or less directly related to his ocular movements, i e , horizontal nystagmus The observations during the period of reappearance of the nystagmus could be brought under a few headings (*a*) lengthening of horizontal lines, (*b*) broadening of vertical lines, (*c*) corresponding distortions, simultaneously in the horizontal and the vertical direction, for closed figures, and, finally, (*d*) monocular diplopia [19]

19 The diplopia itself is just as clearly related to the patient's ocular movements as that in our first case, for the double image disappeared after a latency of fifteen seconds when the original line was rotated into the plane of the nystagmus, and it likewise disappeared when the nystagmus decreased

But, even more than in the first case, the diplopia was only one symptom among a number of deviations from normal perception For this reason, the rare instance of "nystagmus diplopia" cannot be understood without an attempt to define its place among these more general disturbances, for they not only preceded the monocular diplopia during our experiment but persisted, in the sense that they could be evoked again, later on, under special conditions It therefore remains to be seen in which way these general disturbances of perception were related to the transient diplopia and why they appeared successively under the conditions of our experiment

In contrast to the patient's performance before the experiment, these disturbances indicated a much closer correspondence between the shape of the patient's perceptions and the pattern of retinal stimulations The latter, the "proximal" stimuli of Koffka,[20] were originally embedded in a relatively normal functional organization, which restructured the incoming stimulus patterns into single, and fairly undistorted, percepts This was achieved at the price of acuity and with some fluctuation, but, in return, our patient did not see objects as he ought to have seen them That is, he did not see them double or multiple or otherwise distorted according to the continual horizontal movements of his eyes Neither did his visual objects appear to move, except under highly artificial conditions in which the usual points of reference were absent (e g, a single point of light in the dark) An overestimation of the horizontal dimension in judging shapes, sizes and distances may have been present before the experiment But our tests at that time failed to reveal its extent That the patient's vision was always beset with difficulties became evident in his casual remarks during the period immediately following the abolition of his nystagmus Then he complained that with the recurrence of the ocular movements his vision became foggy "again" But it is reasonable to assume that the patient himself became aware of such a generalized impairment of his vision only by means of the contrast with a temporarily improved performance after administration of sodium amytal[21] On the whole, our patient had succeeded in building up a perceptual framework in which the ambiguous stimuli from his retina obtained definite meaning On the other hand, he showed certain deficiencies in this framework which made it different from the one found in the visual organization of normal subjects His ability to maintain constancies for size and form over normal ranges was impaired

Under the effect of the barbiturate, the patient's nystagmus disappeared, and thus his vision became even more efficient, although he had a distinct feeling of strangeness referable to his eyes However as soon as the nystagmus started to reappear, the patient began to show all those disturbances which would be expected to appear if his nystagmus had been acute rather than persistent and chronic (e g, if it had been due to latent nystagmus or produced by a recent lesion).

20 Koffka, K Principles of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc, 1935

21 In numerous other cases of congenital nystagmus we were able to obtain the same temporary improvement in visual acuity by injection of sodium amytal The improvement was both objective (as tested on the Snellen chart) and subjective Indeed, 1 patient felt so much relieved from his ocular distress when under the action of the drug that he expressed a desire to have an injection "at least once a day"

The once-achieved equilibrium of function was abolished, and the patient's perceptions assumed a point to point relationship to the abnormal retinal patterns He thus showed the opposite of the constancy effect of the normal person This effect has been described as an indication of one's ability to depart from such point to point relationships between peripheral stimulus patterns (the proximal stimuli of Koffka), and thus to approximate the "real" object more adequately (A circle appears as a circle even though it is tilted out of the frontal parallel plane It is normally not seen as an ellipse, despite the fact that the retinal projection is an ellipse) It was Thouless [22] who termed these constancy phenomena "regressions to the real object" Disregarding the difficulty of defining the "real" object independently of one's perceptions, we can use an inversion of his term in a merely descriptive manner Our patient's behavior during recurrence of the nystagmus represents a "regression to the proximal stimulus" [23]

However, this regression to the proximal stimulus was not complete Objects—even narrow lines—did not move with the slow phase of the nystagmus but appeared broadened or lengthened, depending on their orientation in the vertical or the horizontal dimension of the patient's visual field Their unitary character as distinct percepts was preserved, except for the episode of diplopia

Furthermore, the broadening and thinning of vertical lines and the lengthening and shortening of horizontal lines did not follow the rhythm or rate of the nystagmus The fluctuation was considerably

22 Thouless, R H Phenomenal Regression to the Real Object, Brit J Psychol **21** 339-359, 1931, **22** 1-30, 1931

23 Regression is to be taken in the spatial sense only, not in the genetic sense We do not imply that at any time during the development of perceptual organization there actually is a point to point correspondence between proximal stimulation and perception Likewise, "proximal stimulus," like "real object," is used here as a mere construct because of its illustrative power The concept of proximal stimuli is obviously an inference from the physiologic theories of sensation They never exist in a biologic sense for the organism itself, unless and until they are perceived, that is, unless they assume the character of objects Conversely, real "visual" objects are characterized by their relative constancy of form, size and color, or their comparative independence of the observer's position, of his inner state, and even to some extent of the sense modality which is called into play It is evident that Thouless' description of constancy phenomena as regressions to real objects involves a logical circle, since phenomenal constancy is the main characteristic of these real objects However, the converse, or regression to the proximal stimulus, may assume a more biologic meaning, for if, and when, constancy is disturbed, or the framework of one's perception impaired, perceptual phenomena are encountered which approximate such functioning as would have to be expected in terms of physiologic hypotheses about peripheral sensory patterns

slower and suggested a staggering of the central effect produced by the rapid, repeated shifts of the stimulations on the retina

The phenomena observed in the Schroder staircase test are of special interest in this connection There, the lengthening and shortening of the base line were synchronized with the changes in configuration, thus testifying to the unitary character of the percept

Significantly, no broadening or lengthening of lines was perceived by the patient when he announced his monocular diplopia This diplopia was the only instance of actual disruption in the formation of perceptual units It appeared as the extreme disturbance, when compared with the other disturbances in this case (viz, elongation and apparent motion), and it took the place of the latter as soon as it occurred As the nystagmus became less pronounced, the diplopia disappeared whereas the lengthening and shortening of lines appeared again

During the days following the experiment the diplopia did not recur However, subsequent observations and experiments revealed that the patient's visual organization was influenced by his nystagmus in many more ways than we had originally expected Some of these phenomena were clearly enhanced and brought to the fore by the injection of sodium amytal, and they thus represented a persistent effect of the brief period of visual disorganization Others had not been noticed during the preexperimental period, yet seemed to be integral features of the patient's individual "mode" of perceiving

For instance, there was a consistent tendency to overestimate horizontal, as against vertical, dimensions Free designs, as well as reproductions of geometric patterns, were characteristically flattened (fig 3) But, in contrast to the "dramatic" period of recovery from the barbiturate, our patient was not aware of those distortions as such They belonged to his framework, or to the "silent" organization, in which his perceptions were embedded [24]

This framework, however, not only was overdetermined (distorted) by abnormal ocular motion but was made deficient by it In the weeks following the experiment, just as during the period prior to the injection, we found evidence of a large reduction in the phenomena of constancy

24 In a separate publication, further instances of such anisotropy of subjective space (inequality of dimensions of visual space) will be offered For our patient, it could be shown that the trend toward deformation was always with him It was abolished only once, under the immediate influence of the barbiturate, when the patient's nystagmus had been arrested During the follow-up period after the experiment, we succeeded in duplicating this situation by presenting visual stimuli in tachistoscopic exposure If the speed of exposure became too high for the nystagmus to play any role, the flattening of patterns disappeared But with a slight variation in the experimental procedure (exposure of objectively "flat" patterns previous to the test—configurations) the latent trend toward distortion was brought out again with any speed of exposure

of visual objects for size, as well as for form and for color In that respect, the patient's nystagmus acted like a reduction screen (Katz [25])—the simple cardboard with a hole in the middle, which immediately abolishes the effects of color constancy Apparently, the nystagmus strips the visual field of the manifold reference points which seem necessary for the obtaining of normal field gradients and constancy effects

Yet, in spite of the abnormality of the patient's framework, the formation of unitary and unambiguous percepts remained possible, unless the patient was stimulated under highly artificial conditions Only when a perceptual context as such is missing (as in dreams, in

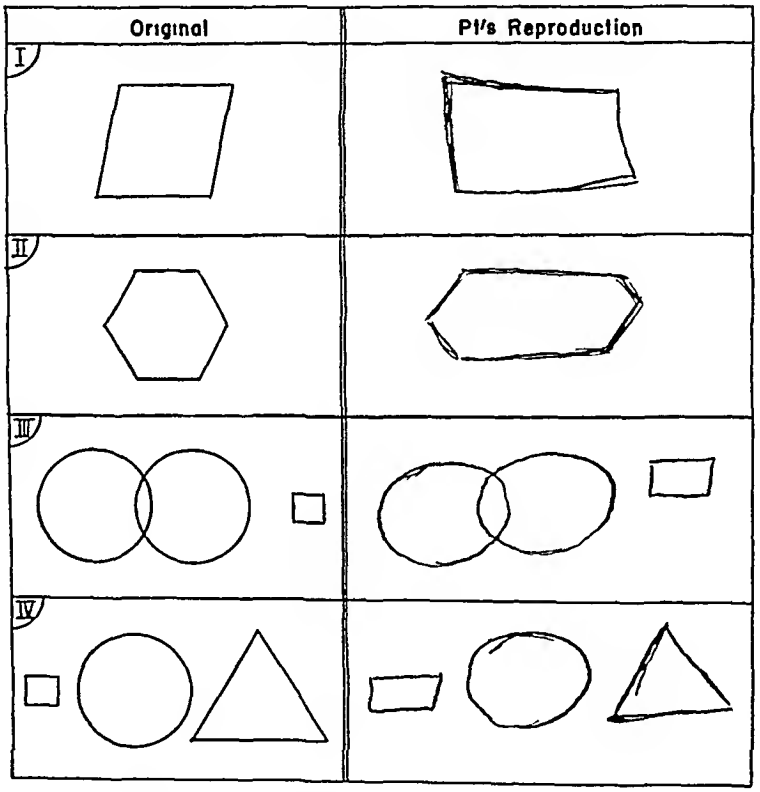

Fig 3—Distorted reproductions of patterns from the Benton visual retention test (Benton, A L Visual Retention Test, Arch Neurol & Psychiat **54** 212-216 [Sept] 1945) made during the period of follow-up study The patient was not aware that he departed from the original patterns

free drawings, in which the patient has neither skill nor experience, or in inspection of small figures and lines) do the perceptions follow directly the "pull" of the congenital nystagmus, and only then do the resulting distortions become pronounced enough to be noted by the patient himself These gross distortions assume three principal forms, which are listed here in decreasing order of degree of disturbance and,

25 Katz, D Der Aufbau der Farbwelt, ed 2, Leipzig, Johann Ambrosius Barth, 1930

conversely, in increasing order of frequency (1) double image formation (only episodic, during recovery from sodium amytal), (2) apparent motion of small stationary objects (fairly common with prolonged fixation of two dimensional geometric patterns), and (3) broadening of vertical dimensions and/or lengthening of horizontal dimensions (relatively most common) Among these three forms of deviant percept formation there obtains a relationship of functional equivalence At any one moment, and in any state of the organism, one, and only one of these distortions appears in the center of the visual field

SUMMARY AND CONCLUSIONS

In 2 cases of transient monocular diplopia, ocular movements during fixations were found to play a major role Whether they actually represent the decisive causal factor in the production of monocular diplopia cannot be established on the basis of the evidence at hand The possibility cannot be ruled out that both abnormal excursions of the eyes and monocular diplopia are consequences of one and the same central impairment in function But our observations illustrate the close interrelationships between perception and movement in the building up of the perceptual world

The ocular movements during fixation impress one as a necessary, but not a sufficient, condition for the development of monocular diplopia If it were a sufficient condition, one would expect to find monocular diplopia much more frequently in cases of recently acquired nystagmus as in miner's nystagmus or in other types of acquired nystagmus In patients who show abnormal ocular movements during fixation, resulting from heteronymous field defects with involvement of the maculas, diplopia is found, but it is apparently limited to binocular vision

In our 2 cases of monocular diplopia there were additional causal factors which make it understandable why the ocular movements produced such extensive distortions of the patient's perceptions The diplopia in these cases represented only one phase in the development of a syndrome of visual dysfunction which has been characterized as a disturbance of the dynamic equilibrium of the perceptual organization (including the oculomotor component) The disruption of this equilibrium in and by itself appears as the precipitating factor It was found in both cases, in case 1 in the form of a cerebral pathologic process and in case 2 as the toxic effect of administration of a barbiturate In that sense the 2 cases are not complementary but analogous

Furthermore, the equilibrium in both cases had certain inherent deviant characteristics which made the development of diplopia after disruption of the balance possible We thus have three levels of causation, which are here summarized in inverse chronologic order

1 The nystagmoid movements during fixation—a necessary condition for monocular diplopia in these cases

2 A disruption of the equilibrium of perceptual functions by a toxic or an inflammatory process—the precipitating factor

3 Finally, in both cases there was the predisposing factor The equilibrium before its disruption by disease or experiment was different from the equilibrium found in normal persons In both cases the visual functions had to cope with abnormal conditions of proximal stimulation In the first case there was congenital convergent strabismus In the second case there was congenital nystagmus Neither of these conditions led to diplopia, since they were genuinely congenital The unitary character of percepts was just as little disturbed as the orientation of one's visual space is influenced by the fact that the lens system gives an inverted picture of the world to the optic tract However, when, in analogy to Stratton's experiment,[26] the functional organization was disturbed, there were indications that the equilibrium in our cases had been achieved under special handicaps For in the period following acute disorganization, or at least modification of functional organization, we encountered a partial regression to the (abnormal) proximal stimulus patterns

Obviously, in these 2 cases the possible range of predisposing factors is not exhausted At least one further condition must be added to that of convergent strabismus and congenital nystagmus namely, the abnormal tonic pull in cases with cerebellar and labyrinthine involvement (Goldstein,[14] Bender[1]) But even in the case of pathologic tonus, it is movement, or at least intended movement, of the receptors which accompanies changes in perceptions

In all these cases generalized changes in perceptions can be found embedding the monocular diplopia Such systematic changes are of a higher explanatory value than any monosymptomatic examination could reveal A full understanding of perceptual disturbances seems impossible without an attempt to observe the total organization, with its interrelationship of perception and movement For that reason, a complete survey of single cases seems preferable to studies of relative frequencies of symptom associations At present it is difficult to make exact measurements of visual disorder in cases of this kind But an eventual explanation of the major perceptual disturbances would take one a long way toward an understanding of normal perceptual function

1192 Park Avenue, New York

26 Stratton, G M Vision Without Inversion of the Retinal Image, Psychol Rev 4 341-360 and 463-481, 1897

USE OF CURARE IN OIL IN TREATMENT OF SPASTICITY FOLLOWING INJURY OF THE SPINAL CORD

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WEST,[1] Burman,[2] Bennett [3] and others described the use of preparations of curare in treatment of various syndromes exhibiting spasticity, tremor and rigidity They found that curare diminished hypertonia, tremor and involuntary movements The clinical effect, however, was usually transient and therefore of questionable therapeutic value Denhoff and Bradley,[4] in a group of spastic children, found that the initial period of response to effective doses was characterized by masked facies, head drop and mental confusion After these unpleasant reactions had worn off, the useful clinical effect became evident These therapeutic experiments were carried out with aqueous solutions of the drug, used either intravenously or intramuscularly

In the present study a group of patients showing intense spasticity accompanying injury to the spinal cord were treated with aqueous solutions of curare Eleven patients with extreme spasticity were chosen from a large group Of these 11, 9 had complete paraplegia and 2 had demonstrable voluntary function masked by spasticity These patients were given aqueous solutions of curare intramuscularly every four days The results were in accordance with the observations of the previous investigators Excellent relaxation was obtained, but at its peak it was accompanied by blurred vision, diplopia, general weakness and dizziness The desired effect reached a peak rapidly and subsided in four or five hours, although in several cases a clinical effect was observable up to eighteen hours The side effects likewise disappeared rapidly and without residual Because of these side effects the practical value of the relief was limited, since the patient could not carry out his usual educational and social activities while they lasted

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From New York Neurological Institute and Department of Neurology, Columbia University College of Physicians and Surgeons

1 West, R Curare in Man, Proc Roy Soc Med **25** 1107-1116 (May) 1932

2 Burman, M S Clinical Experiences with Some Curare Preparations and Curare Substitutes, J Pharmacol & Exper Therap **69** 143-148 (June) 1940

3 Bennett, A E Clinical Investigations with Curare in Organic Neurologic Disorders, Am J M Sc **202** 102-112 (July) 1941

4 Denhoff, E, and Bradley, C Curare Treatment of Spastic Children Preliminary Report, New England J Med **226** 411-416 (March 12) 1942

USE OF OILY SUSPENSIONS

The objection to the use of curare, then, lies in its evanescent effect and concomitant side reactions In this investigation, various menstruums were tried in an attempt to overcome these handicaps A suspension in peanut oil and white wax U S P, similar to that used by Romansky and Rittman,[5] proved most suitable of the preparations tried

Method of Preparation—Crystalline *d*-tubocurarine chloride[6] was suspended in a peanut oil—white wax mixture mechanically The dosage was determined by clinical assay A 3 per cent suspension of tubocurarine in a mixture of 4 per cent white wax in peanut oil appeared optimal

This suspension was used routinely every four days with the aforementioned 11 patients The average dose was 1 25 ± 0 25 cc, given deep in the gluteal muscles The following cases illustrate the results achieved

REPORT OF CASES

CASE 1—A man aged 34 for twelve months had suffered from a traumatic lesion at the second thoracic level of the cord due to a gunshot wound A laminectomy within forty-eight hours after injury revealed an edematous, discolored spinal cord in continuity Within three months there was return of crude sensation, and voluntary power was noted in the left foot Voluntary power increased regularly, and within nine months the patient could move all muscle groups However, the return of motor control was accompanied by increasing spasticity in flexion Ulceration of the mesial aspects of both knees, secondary to adductor spasm, supervened Fibrosis and contracture at the knee joints followed the prolonged spasm (fig 1) The patient complained bitterly of pain and attempted suicide in depression over the progress of events

Use of curarine in oil was started, and a dose of 1 25 cc was arrived at by estimation of the clinical effect The patient began to note relaxation of spasm in forty-five minutes and maintained it for an average of seventy-two hours (fig 2*A* and 1*B*) His subjective symptoms disappeared at the same time He was encouraged to move about freely and to exercise actively He noted no increase in paresis during his periods of relief from spasticity Physical therapy was started and vigorously pursued during these periods The ulcerations of the knee region healed spontaneously with relaxation of adductor spasm Muscle tone and volume improved Over a period of two months there was a perceptible decrease in spasticity over and above the effect of the drug

CASE 2—A man aged 24 had suffered from a gunshot wound at the first thoracic segment of the spinal cord for ten months Laminectomy after injury revealed bony fragments compressing the dura, with an edematous, bruised cord Complete paralysis was followed by rapid, spontaneous improvement over six months, with complete sensory return and about 70 per cent motor recovery Intense spasticity appeared with voluntary return of function, and at ten months the patient suffered from severe spasticity in flexion with pronounced contractures at the knee joints

Curarine in oil was administered in increasing doses A dose of 1 cc appeared optimal The duration of effect averaged seventy-eight hours and was not charac-

5 Romansky, M J, and Rittman, G E Method of Prolonging Action of Penicillin, abstracted, Science **100** 196-198 (Sept) 1944

6 The tubocurarine was supplied by E R Squibb & Sons, New York

terized by any toxic signs or symptoms During periods of relaxation of the spasticity the patient had excellent motor power, limited severely by the contractures at the knee joints Intensive physical therapy was started with active and passive exercises The contractures were rapidly reduced, and muscle strength and volume improved perceptibly

Case 3—A man aged 33 had sustained a complete transection of the cord at the fifth thoracic segment as a result of a gunshot wound one year previously He suffered from severe spasticity, and a mass reflex was induced by the slightest stimulus Braces could not be fitted because of this condition nor could the patient be taken out of bed Fixation of joints became more and more pronounced Administration of curarine in oil was started and the dosage adjusted at 1 3 cc

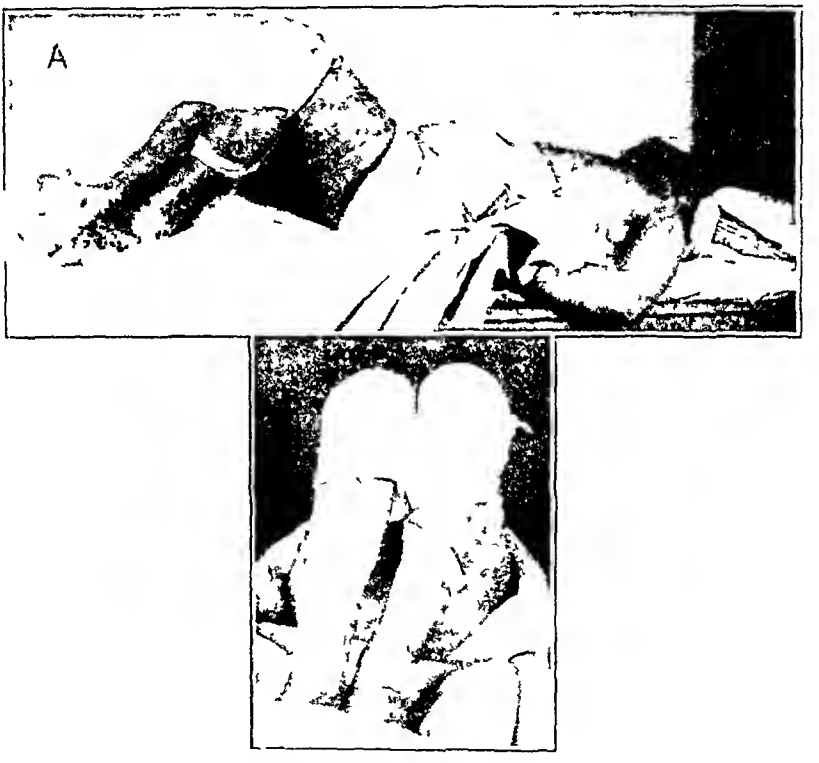

Fig 1 (case 1)—*A*, position of spasticity in flexion maintained by the patient prior to treatment, *B*, adductor spasm prior to treatment

The duration of effect was sixty-three hours During periods of relief physical therapy could be carried out without initiation of mass reflex movements It was thus possible for the first time to work on the patient's joint fixations and to prepare him for the use of braces later

Case 4—A man aged 24 had sustained a complete transection of the cord at the fourth thoracic segment as a result of a gunshot wound nine months previously The patient had decubitus ulcers over the trochanteric and sacral regions and on the heels Healing was prevented by regularly occurring mass movements Contractures at the knee and the hip joint became pronounced Physical therapy could not be carried out because of the reactive spasm and the mass reflex movements

Administration of curarine in oil was started, and 1 5 cc was found to be the optimal dose The patient showed clinical relief for periods up to sixty-eight hours Epithelization was prompt on cessation of the constant friction over the granulating areas The contractures at the joints were gradually reduced with passive exercises The patient was helped out of bed to participate in ward activities

COMMENT

It is noteworthy that none of the undesirable side effects of curare therapy were observed in these cases During the adjustment of dosage levels occasional slight blurring of vision was noted At all times the patients were able to carry out their usual activities without handicap The low levels of curare in the circulating blood probably accounted

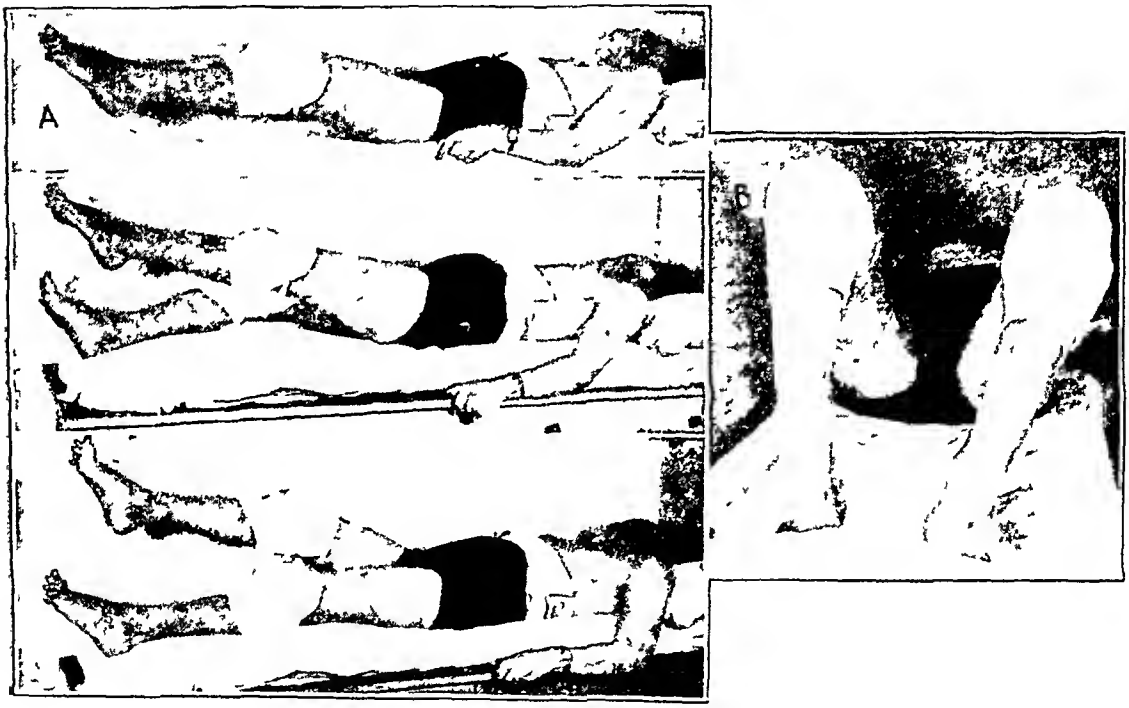

Fig 2 (case 1) —Patient twenty-four hours after injection of suspension of curarine in oil *A*, full voluntary extension of the lower extremities, with normal range of motion, *B*, reduction of adductor spasm

for this phenomenon Since determination of levels in the blood was not feasible during this study, the exact mechanism of the prolonged effect of curare is not known

In this small series it was noted that the relaxation was more striking in the paretic than in the paraplegic patients No explanation of this fact can be given at present

Continued studies on the clinical use of long-acting preparations of curare are contemplated Their use in the treatment of other diseases exhibiting spasticity rigidity and tremor will be the subject of future investigation

SUMMARY

A suspension of curare in a mixture of peanut oil and white wax afforded good relaxation of muscle spasm of up to three days' duration in a group of patients with injuries of the spinal cord Effective reduction of spasticity was not accompanied in any case with the usual effects of curare, such as severe changes in accommodation and head drop Slow absorption, with avoidance of unpleasant side effects, greatly enhances the therapeutic value of the drug

1 A suspension of *d*-tubocurarine chloride in a peanut oil–white wax mixture yields a slow action curare effect, lasting in some instances up to three days

2 The action of such a preparation is not characterized by the concomitant appearance of the undesirable side effects of curare

3 The use of curare in oil in relief of spasticity following injury to the cord seemed of therapeutic value in a series of 11 cases of which 4 are cited in this paper

4 The value of drugs which afford relaxation of muscle spasm in permitting physical therapy is stressed

5 The effect of curare in oil on patients with some voluntary function masked by spasticity seemed more dramatic than the effect seen in paraplegic patients

6 The effect of curare in oil in treatment of syndromes exhibiting spasticity, tremor or rigidity will be further explored

Mr Joe V Tucker and Mr Robert Felberg gave technical assistance in this study

News and Comment

ORGANIZATION OF EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

Twenty-seven prominent civilian and military electroencephalographers from several states met at the Graduate Club of the Institute of Living in Hartford, Conn, on March 1, 1946, to organize the Eastern Association of Electroencephalographers Formed for the purpose of promoting research in the field, the association plans to pool scientific information concerning the neurophysiology and clinical application of electroencephalography

Lieut Comdr Robert S Schwab (MC), U S N, of the United States Naval Hospital in Boston, was elected chairman of the association, and Dr Charles W Stephenson, of Hartford, was elected recorder

One of the immediate projects of the group is to approach the American Physiological Society, the American Neurological Society, the American Psychiatric Association and the Council on Physical Medicine of the American Medical Association on the matter of establishing a joint committee among the several organizations for the purpose of considering the desirability and means of establishing minimum standards for approved electroencephalographic laboratories Chairman of the committee appointed to pursue this project is Dr Hallowell Davis, associate professor of physiology at Harvard University, members are Dr Paul A Hoefer, associate professor of neurology at Columbia University, and Dr Margaret Kennard, assistant professor of neuropsychiatry and neuroanatomy at New York University

Dr Wladimir T Liberson, director of the Physiological Research Laboratory at the Institute of Living, Hartford, Conn, and professor at Ecole des Hautes Études, New York, was appointed chairman, and Dr Leslie F Nims, assistant professor of physiology, Yale University, and Dr Margaret B Rheinberger, who is in charge of the electroencephalographic laboratory at Montefiore Hospital, New York, were appointed members of the organization and program committee

Attending the meeting were Dr John A Abbott, Dr Mary A B Brazier, Dr Hallowell Davis, Mr and Mrs Albert M Grass, Dr Milton Greenblatt, Lieut Comdr Herbert I Harris (MC), U S N R, Dr Hudson Hoagland, Lieut Comdr, Robert S Schwab (MC), U S N, and Dr Wolfgang Sulzbach, of Boston, Dr Pablo Anglas, Dr Santiago Castillejos, Dr Wladimir T Liberson and Dr Charles W Stephenson, of Hartford, Conn , Lieut Charles E Henry (MC), U S N R, of Newport, R I , Lieut David G Jones, M C, Army of the United States, Lieut Curtis Marshall (MC), U S N R, and Dr Charles I Kaufman, of New London, Conn , Dr Milton H Kibbe, of West Springfield, Mass , Dr Margaret Lennox and Dr Leslie F Nims, of New Haven, Conn , Dr Donald B Lindsley, of Providence, R I , Dr Abraham Mosovich, of Washington, D C , Dr Paul A Hoefer and Dr Margaret B Rheinberger, of New York, Lieut Russell Anthony (MC), U S N R, and Comdr William F Murphy (MC), U S N R

The newly formed association will meet bimonthly, with the seminar type of meeting preferred The second meeting is scheduled to be held at the Graduate Club of the Institute of Living at 1 o'clock on Friday, April 12, 1946, at which time a draft of the constitution and by-laws will be presented by the organization

and program committee Also, military experiences in electroencephalography will be discussed by Dr Milton H Kibbe, who will speak of the Army work, and Dr Charles B Henry, who will report on Navy data

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

The spring examinations for certification by the American Board of Psychiatry and Neurology will be held in Chicago on May 23, 24 and 25 at the Illinois Neuropsychiatric Institute There will also be a one day examination in San Francisco on June 25 Acceptance of applications for these examinations ended March 13

Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Psychiatry and Psychopathology

DEPRESSION — THE OEDIPUS CONFLICT IN THE DEVELOPMENT OF DEPRESSIVE MECHANISMS EDITH JACOBSON, Psychoanalyt Quart **12** 541, 1943

Jacobson reports the results of psychoanalysis in the case of a woman aged 24 who had a depression at 3½ years of age and again at puberty and finally one which brought her for psychoanalysis Her father suffered from severe depressions Jacobson places her condition in the manic-depressive group, but it was difficult to decide whether it might not be a severe anxiety hysteria with borderline depressions Analysis showed that at the age of 3 there was the beginning of a normal Oedipus situation In the next half-year she suffered a series of traumatic incidents, among which was contact with her father's penis, which aroused her genital sensations intensely and prematurely and led her to expect a gratification from him similar to the gratification which she obtained from the frequent enemas given by her mother She also had a frightening experience with a psychotic maid and recalled her mother's pregnancy with her brother This series of traumatic incidents ended in a psychic collapse at the age of 3½ years As a result of these incidents she felt disappointed by her father, and in bitter hate she turned away from him and back to her mother Here, again, she was disappointed because the mother loved only the baby In her disappointment and hostility she tried to escape into a narcissistic withdrawal and kill her need for love by becoming absolutely self sufficient and independent In this goal she failed because of her intense ambivalence, as it was expressed in her fantasies of the primal scene—her wishes for participation in the sadistic fight of her parents and for their incorporation and annihilation In vain she attempted to ward off her destructive impulses by identifying herself with the image of her good parents and by rebuilding her love relationship to them The outcome of this conflict was her first depressive collapse From that time she shifted her ambivalent desires from one parent to the other, without being able to establish a firm relationship with either In her most balanced periods she found some security in her dependent but reliable bondage to her mother, competing with her brother by being the oversubmissive child She invited her father's appreciation by her intellectual superiority

This aggressive desertion of one parent for the other, with its guilty reactive sadomasochistic love, seems to be typical of the Oedipus situation in cases of the manic-depressive psychosis

After disappointment in the homosexual object the patient breaks away aggressively and approaches a heterosexual object Unable to carry out this attachment because of ambivalence, he vainly attempts to return to the homosexual object This attempt fails because of ambivalence Then the patient goes into a depression

PEARSON, Philadelphia

INVESTIGATION AND TREATMENT OF ENURESIS IN THE ARMY PRELIMINARY REPORT ON 277 CASES P L BACKUS and G S MANSELL, Brit M J **2** 462 (Oct 7) 1944

Backus and Mansell made a study of the results of treatment of 277 unselected patients with nocturnal enuresis consecutively admitted to a military hospital during a period of eight months A complete routine physical examination revealed no abnormality in 92 06 per cent of the patients A cystometric examination was performed on 232 patients The ages ranged from 14 to 45, with an average of 21 33 years The intelligence rate, based on the matrix test, ranged from S G I

to V, with a mean of S G III plus A history of nocturnal enuresis from infancy was elicited from 75 81 per cent of the patients From the psychiatric study, the men were classified under six personality types timid, 48 01 per cent, average, 27 07 per cent, compensatory aggressive, 10 49 per cent, purely aggressive, 6 14 per cent, psychopathic, 5 77 per cent, and predominantly obsessional, 2 52 per cent It was noted that the older the patient and the poorer the intelligence, the greater the difficulties in treatment Follow-up observations on 40 patients in the series showed that 31 were returned to full duty with satisfactory bladder control and 4 to light duty with satisfactory bladder control, 2 were discharged, and 3 were readmitted for further treatment The authors concluded that suitability of such patients for treatment in the army is dependent on the following factors the age, preferably under 30, fair intelligence, bladder capacity of more than 300 cc and water pressure of 60 cm, and evidence of voluntary powers of relaxation

ECHOLS, New Orleans

Meninges and Blood Vessels

TUBERCULOUS MENINGITIS REPORT OF A CASE WITH CLINICAL RECOVERY DOMINGO UNCHALO, Rev med d Hospital de La Plata **1** 39 (Oct-Dec) 1944

Unchalo presents a case of recovery from tuberculous meningitis three years after the illness The man was 28 years of age at the beginning of his acute illness on Nov 26, 1941 The clinical picture was that of acute meningitis, with 96 cells in the clear, but mildly xanthochromic, spinal fluid There were 68 per cent lymphocytes and 32 per cent polymorphonuclear leukocytes The sugar of the spinal fluid measured 38 mg and the chlorides 500 mg per hundred cubic centimeters Five tubercle bacilli were found in the centrifuged spinal fluid No cultures or animal inoculations were made The reaction was positive to tuberculin A roentgenogram of the chest showed old sclerotic and calcified lesions The patient was treated with intrathecal injections of gold salts The author believes that his patient had tuberculous meningitis

SAVITSKY, New York

Diseases of the Brain

POSTCONTUSIONAL HEADACHE ERICH GUTTMANN, Lancet **1** 10 (Jan 2) 1943

Little is known of the factors which lead to the development and persistence of the common after-effects of head injury (headache, giddiness and lack of concentration) in some persons and not in others Guttmann reports on 200 patients representing consecutive admissions for head injury for whom the presence or absence of headache was noted in the records

The duration of post-traumatic amnesia, assessed at the time of discharge from the hospital, was used as an indicator of the severity of the injury For 179 of the patients the data were as follows

	Duration of Post Traumatic Amnesia	No of Patients
Group O	5 min	33
Group A	1 hr	85
Group B	24 hrs	39
Group C	7 days	19
Group D	Over 7 days	3

Less than one-half the patients complained of headache when they awoke from unconsciousness, and the proportion grew smaller the longer the unconsciousness lasted This may be due to the inability of patients with severe injury to observe and describe their sensations Of 166 of these patients, 76 complained of headache (mild or severe) at one time or another during their stay in the hospital Only 154 were examined at the time of discharge, and of these, 32 had headache At a time when it was expected that the patients would be fit for work again, 38 per cent

of them had headache At the end of three months only the patients who had returned to work were examined, and here, again, the incidence of headache was 21 per cent Six months after the injury it was 18 per cent

Up to and including the time of the first follow-up examination, the incidence of headache among patients with milder injury was persistently higher than that among patients with severe injury Three to six months later this difference disappeared This observation seems to point to factors not immediately connected with the mechanical injury If the duration of the post-traumatic amnesia is a rough measure of the severity of injury, one would expect some correlation between symptoms and severity independent of the lesion in a given case The 23 patients who had headache six months after injury were examined clinically, in the hope of shedding light on this question

In this group of 23 patients age was not considered an important factor Roughly, 25 per cent were under 20 years of age, 25 per cent were over 50, and the rest were between 21 and 50 years old One patient was excluded because the presence of acute otitis media explained his headaches Six patients revealed that they had had similar headaches all their lives Two patients reported cessation of their headaches during the time of observation One patient, an elderly spinster, had received medical care for years for nervous exhaustion Another patient, a nervous child, never complained of headache which an overprotective mother insisted was present Another patient was a defective, emotionally unstable girl, who had had variable nervous symptoms all her life Nine patients presented fairly obvious psychogenic motivation Guttmann points out that this does not exclude an organic basis, but that since most patients with similar injuries do not complain of headache, it is fair to assume that either the symptom itself or the patient's attitude toward it is determined by demonstrable psychologic factors rather than by the hypothetic organic basis In only 2 cases of the group was no cause for the persistent headache discovered

It seems possible, with active treatment, to discharge 80 per cent of patients from the hospitals free of complaints Less than one-half the patients discharged are left with some liability to headache This predisposition is psychosomatic, that is, psychologic factors are as important as physical factors in precipitating headache It is the opinion of the author that they are more important

SANDERS, Philadelphia

SULPHANILAMIDE POISONING WITH CEREBRAL MANIFESTATIONS HOWARD REED, Lancet **2** 535 (Oct 21) 1944

Reed describes the case of a 3 year old girl who took sulfanilamide by mouth when left alone for three hours She was found unconscious and stiff in hyperextension, with the right arm flexed She alternated between quiet and excited periods, with grotesque convulsive movements or thrashing from side to side, during the first twelve hours She then was able to recognize a friend and improved slowly but steadily during the next several days

Reed compares the dilated pupils, teeth grinding, rigidity and convulsive movements seen in this girl with the same signs found by Hawking in rabbits and cats after similar doses of a sulfonamide compound (*Lancet* **2** 1019, 1937) This child's restlessness was also similar to that seen in a case of overdosage of a sulfonamide drug reported by Cutts and Bowman (*New England J Med* **225** 448, 1941)

MCCARTER, Boston

QUININE BLINDNESS I S MCGREGOR and ARNOLD LOEWENSTEIN, Lancet **2** 566 (Oct 28) 1944

McGregor and Loewenstein describe the case of a man aged 37 who had had malaria twelve years previously and had been treated with quinine, with no trouble other than transient tinnitus and deafness He was given 30 grains (1 95 Gm) of quinine dihydrochloride every two hours for a recrudescence of fever In thirty-

six hours he was blind and deaf, the deafness cleared quickly, but the amaurosis improved only slightly The retinas were milky in appearance, and there was a cherry red spot at each macula Treatment was with purgation with magnesium sulfate, protein shock and forced fluids and dextrose After several days administration of a preparation of vitamin B complex and ascorbic acid was added The retinal arterioles became narrow and the optic disks rather pale The pupils reacted slightly to light, but colors could be recognized on Ishihara plates, though the patient could not read numbers two or three weeks after onset The visual fields were carefully tested and found to be constricted, but not so much so as the responses would indicate It was found that they were sievelike, in that several scotomas deprived them of uniform perceptual quality Visual acuity was 6/60 in the right eye and 6/5 in the left eye Several months later the patient had learned to use his vision more skilfully (visual acuity 6/12 in the right eye and 6/24 in the left eye), but for practical purposes he was blind

The authors attribute the milky appearance of the retina to ischemia caused by thromboses, due, in turn, to toxic proliferative changes in the arteriolar endothelium Quinine also acts on the ganglion cells

The authors urge prevention by careful use of quinine, not more than 30 grains (1 95 Gm) daily, and not this much until administration of small doses has ruled out sensitivity When blindness has occurred, therapy aims to effect early and vigorous exchange of fluid Locally, paracentesis of at least one eye was tried in this case, and the procedure is advised in addition to general methods Vitamins are used to facilitate oxygenation in the retina

McCarter, Boston

Significance of the Pupillary Light Reflex in Diseases of the Nervous System J Candido da Silva, Arq de neuro-psiquiat, São Paulo **1** 271 (Dec) 1943

In 1753 Robert Whytt first showed that the pupillary reaction to light is a true reflex The author insists that an Argyll Robertson pupil is always bilateral The pupils are considered miotic when they are less than 2 mm in diameter He found the Argyll Robertson pupil in only 7 of 300 patients with dementia paralytica The presence of this pupil in cases of this disease indicates a poor prognosis Six of the 7 patients died, and 1 failed to respond to treatment In 2 patients pathologic responses to light occurred as an isolated symptom, without evidence of syphilis or any other disease The author emphasizes the inadvisability of using the term Argyll Robertson pupil indiscriminately

Switsky, New York

Neuropsychiatric Aspects of Manganese Intoxication Isaac Horvitz and Enrique Uiberall, Rev neurol de Buenos Aires **9** 1 (Jan.-March) 1944

Horvitz and Uiberall report neuropsychiatric changes in 64 cases of manganese poisoning among workers in manganese mines in the north of Chile The patients from a group of 800 workers, were observed over a period of three years, 39 were examined personally The manganese, from manganese oxide, readily becomes pulverized and was found in the atmosphere of the mines in concentrations as high as 250 mg per cubic meter The time of exposure to the manganese before symptoms appeared varied from forty-nine to four hundred and eighty days, with an average of one hundred and seventy-eight days

Five of the personally observed patients had a prodromal period, with headache, weakness, pain in the muscles, sialorrhea and somnolence Seventeen of the other 34 patients had definite mental changes, 12 had neurologic signs and 5 did not Fourteen had a relatively benign manic syndrome, the other 3 exhibited manic excitement with irritability Mental symptoms occurred in 34 of the 64 patients The most characteristic mental change was a manic syndrome with elation and a peculiar impulse to sing, run, dance and work at a rapid pace There was no confusion or evidence of intellectual enfeeblement during the acute psychosis, all the patients showed insight into their morbid behavior Three patients had

visual hallucinations (zoopsia), which were terrifying in only 1 case, all the patients had amnesia for the episode The manic syndrome showed less pronounced elation, less flight of ideas and definitely less bizarre mental content than the classic manic psychosis Only 1 patient, during the height of the illness, showed some aggressiveness, with antisocial tendencies These episodes lasted from ten to twenty days in most cases, and never longer than seven weeks Persistent mental changes were rare but did occur The authors note that persistent enfeeblement and euphoria were present one and one-half years after the acute psychosis in 1 patient Another had recurring fugue reactions for six months

Forty-one of the 64 patients showed definite neurologic changes In the patients with concomitant mental changes, the neurologic manifestations usually appeared a few weeks to three months after the mental symptoms In only 1 patient did mental changes appear one month after the neurologic symptoms All the patients showed involvement of the extrapyramidal system Eighteen patients exhibited concomitant signs referable to the pyramidal tract The clinical picture was that of paralysis agitans Hypokinetic phenomena predominated, 1 patient exhibited choreiform movements and 2 tremors Paresis of convergence was noted twice and defective pupillary contractions during accommodation once Perioral tremors with voluntary movements were observed in 3 patients and constant hyperexcitability of the facial muscles in 3 others Sensory changes were noted in 7 patients, involving the whole body in 2, they were not of an organic pattern The course of paralysis agitans was much more rapid after manganese poisoning than after encephalitis, there was no long interval of freedom after exposure to the manganese Most of the patients showed progression toward a definite picture of paralysis agitans, but the condition of some did not progress Actual regression, though rare, was observed

SAVITSKY, New York

Diseases of the Spinal Cord

THE DIAGNOSIS OF POSTERIOR HERNIATION OF THE LUMBAR INTERVERTEBRAL DISKS
DONALD MUNRO, New England J Med **232** 149 (Feb 8) 1945

Munro presents data on two parallel series of cases in which the history and the results of physical examination might generally be considered to justify a diagnosis of herniation of the nucleus pulposus from a ruptured lumbar intervertebral disk In one series, of 28 cases, a herniation was proved to have been present by operation and by examination of the removed material in all but 3 cases, in which unmistakable and characteristic myelographic deformities were present In the other series, of 41 cases, the following diagnoses were made ruptured intervertebral disk, 13 cases (proved wrong by operation in 10), compression of a nerve root by a small dural envelope or local scar resulting from a fractured lumbar vertebra, 19 cases (in 14 of which the diagnosis was verified by operation), questionable radiculitis, the cause of which was not apparent, 4 cases (verified by operation in all), congenital defect without other demonstrable disease, 2 cases (verified by operation in both), and strained back, 3 cases (verified by operation in 1) Of 9 of the cases in which the clinical diagnosis was not verified by operation, an abdominal aortic aneurysm was visible roentgenographically in 1 The myelographic evidence was negative for the lesion in this case In 1 case four myelograms were negative, an operation was not performed in spite of a "typical history" In 1 case there was an unquestionably positive myelogram, and operation was advised but refused In 5 cases herniated disks had previously been removed elsewhere, only to have the symptoms recur in four to eleven months In 2 of these cases the myelogram was abnormal but not characteristic of herniation, and in 1 case it was normal All 5 patients are awaiting a second operation In the last (ninth) case the history and physical examination suggest a herniated disk and the myelographic evidence is questionable, but the patient has refused operation

From an analysis of these data, Munro concludes that a clinical history and an examination that even includes a study of the cerebrospinal fluid are not enough

to justify an indisputable diagnosis of posterior herniation of a lumbar disk An unequivocal recommendation of operation as a method of treatment is equally unjustifiable in such circumstances If, however, one can demonstrate a sensory deficit that corresponds to the peripheral distribution of a low lumbar or an upper sacral root, together with atrophy and loss of the ankle jerk in the same leg, a diagnosis of irritation or compression of the particular root is justified

If, in addition, there is a history of intermittent attacks of pain in the back with radiation to any part of the leg, especially to the lower portion, which is associated with initiation or increase of the typical pain by coughing, sneezing or straining or by motion of the back or lifting, and if these attacks started after an injury to or strain of the back, a lifting strain or a fall, a posterior herniation of either the fourth lumbar or the lumbosacral disk must be seriously considered as a cause of radiculitis This cannot be regarded as approaching a certainty, however, unless confirmed by other, and more accurate, data Additional symptoms and signs, whether present or absent, neither strengthen nor weaken this possibility A positive straight leg-raising or Lasegue test, limitation or loss of motion of the back, a change in the lumbar curve, spasm of the erector spinae muscles and local tenderness in the lumbosacral area indicate only that the patient has some trouble with the lower part of his back, the lumbosacral roots or the cauda equina and neither confirm nor deny the diagnosis of herniation

A history and examination such as that previously given, if accompanied with partial or complete dynamic block or with an increase in the total protein content of a sample of cerebrospinal fluid properly collected from below the level of the block or with both, justify a diagnosis of irritation or compression of any part or all of the cauda equina and a probable diagnosis of either an intraspinal tumor or a midline posterior herniation of a lumbar disk Final differentiation must at least await myelographic study, and in many cases operation

The level of herniation, if one is present, is usually not determinable on the basis of clinical data alone, and it is entirely out of the question to diagnose and to localize multiple herniations without adequate preoperative visualization of the lower subarachnoid space

Certain diagnosis, concerning both the presence of a herniation or herniations and the level, depends on adequate visualization of the lumbosacral subarachnoid space by an opaque contrast medium So far, a 20 per cent solution of skiodan has proved satisfactory for this purpose

Clinical examinations lay the groundwork for suspecting the presence of posterior herniation of a lumbar disk Myelographic examination with a contrast medium proves or disproves its presence, determines the level of the herniation and leads to a minimal amount of surgical intervention should this be indicated

GUTTMAN, Philadelphia

Peripheral and Cranial Nerves

PRESSURE PALSY IN THE PARALYSED LIMB W LEWIN, Lancet **2** 756 (Dec 18) 1943

Lewin reports 5 cases of popliteal nerve palsies in patients with traumatic injuries of the brain and cord The clinical separation of the peripheral nerve injury from the disease of the central nervous system is often difficult or impossible Clinical examination shows, theoretically, a sensory loss over the distribution of the affected nerve and a flaccid paralysis, as against a spastic paralysis of the surrounding muscles There would be a "continued absence of power in the peroneal and anterior tibial muscle groups of a limb otherwise recovering, a disproportionate rate of wasting of these muscles in the paralyzed limb', failure of these muscles to participate in the mass reflex in a case of paraplegia, failure to elicit this reflex by stimulating the dorsum of the foot or outer side of the leg The presence of a plaster sore or bed-sore over the head of the fibula is always highly suggestive" But one cannot dogmatize on clinical evidence alone, so electromyo-

graphic studies are made Lewin feels that the "presence of fibrillation action potentials is evidence of a lower motor neurone denervation of the muscles concerned, it does not occur in an upper motor neurone lesion"

The sweating test was quinizarin (1,4-dihydroxyanthraquinone) was also employed to show absence of peripheral innervation This is particularly helpful in cases of lesions of the cauda equina, in which the sweat fibers have already left the cord and are now distributed with the peripheral nerves Of the two tests, the sweating test was the chief diagnostic aid, in 4 of the 5 cases it was more helpful than the electromyogram

Since most of the patients are transported in war areas, under conditions which do not allow optimum care, the author suggests the application of a cotton pad over the lateral aspect of the knee of the paralyzed leg McCarter, Boston

Treatment, Neurosurgery

Part-Time Protective Environment and Working Parole as an Adjuvant in the Treatment of Alcoholism Joseph Thimann, New England J Med **231**:9 (July 6) 1944

Thimann reports the case histories of 3 patients who were addicted to alcohol These patients were subjected to the so-called conditioned reflex method of treatment and to a plan whereby they were able to work but remained as boarders in an institution The author stresses the beneficial role of a part time protective environment, which should be continued for about a year, as an adjuvant in the treatment of addiction to alcohol This plan should be supplemented with the conditioned reflex treatment, psychotherapy, social adjustments and physical therapy

Guttman, Philadelphia

Shock Therapy in the Involutional and Manic-Depressive Psychoses J A Bianchi and C J Chiarello, Psychiatric Quart **18** 118 (Jan) 1944

Bianchi and Chiarello treated 87 patients with involutional melancholia and 134 patients with manic-depressive psychoses with metrazol and electric shock Metrazol was used in treatment of the majority of both types of patients Sodium citrate in large doses was given to prevent thrombosis and to shorten the initial clonic phase, in which it was noted the complications of fracture occurred A series of fifteen to twenty convulsions were induced, either with the drug or with the electric current

Of the patients with involutional psychoses, 58.6 per cent left the hospital improved Of those who did not recover, 75 per cent were of the paranoid type The patients with involutional melancholia whose symptoms had existed for less than two years did better with shock treatment than those who had been sick longer, but duration of symptoms had only a slight effect on the results for the patients with manic-depressive psychosis Of the latter, the depressed patients did better than the manic patients Of both the patients with involutional melancholia and the patients with manic-depressive psychosis who left the hospital after treatment, 90 per cent did so in two months or less

The only complications of therapy included fracture of the humerus, in 4 patients, and abscess of the lung in 2 patients, the latter occurring before sodium citrate was used with metrazol These 6 patients were not included in the series, since their treatment was not completed Two patients with crush fracture of the vertebrae were included, since their fractures were not discovered until routine examination at the end of the course of treatment

McCarter, Boston

Effect of Pethidine [Demerol] on Pain in Neurological Cases Gerald Fitzgerald and Brian McArdle, Lancet **1** 296 (March 6) 1943

Pethidine, the hydrochloride of the ethyl ester of 1-methyl-4-phenyl piperidine 4-carboxylic acid, was given to 12 selected subjects with severe pain arising from

various neurologic conditions The pain was (1) of central origin, (2) of peripheral origin or (3) operative and postoperative The drug was given by the oral, the subcutaneous or the intravenous route The dose varied from 50 to 100 mg Intravenous injections were given slowly, over a period of two to four minutes The effects were judged by the patient's comments and by clinical observations

Ten of the patients received the drug intravenously—100 mg being given to 8 patients, 66 mg to 1 patient and 150 mg to 1 patient Four patients were given the drug subcutaneously—100 mg being administered to 3 patients and 50 mg to 1 patient Four patients received the drug orally—3 having 50 mg and 1 100 mg All but 1 patient, who suffered from a painful phantom limb, experienced some degree of relief from pain In 8 patients the response was excellent Complete relief from severe pain was obtained for a number of hours With 1 patient the result was striking In a child of 12 years a severe headache developed during an encephalographic examination, the pain was quickly relieved by intravenous injection of 66 mg of the drug, and the rest of the procedure was carried through without discomfort In 3 of the 12 patients relief was considerable, but pain was not entirely abolished, and the duration of relief was not more than four hours

Giddiness, faintness, sweating, blurring of vision, nausea, tremulousness and anxiety were the various side effects occurring among 7 of the 10 patients given the drug intravenously These features were transitory in all but 2 patients, in whom they persisted for fifteen and thirty-five minutes, respectively

The relief gained with Pethidine was compared with that following administration of ¼ grain (16 mg) of morphine to 7 patients All received considerable relief from the drug, but it was less definite and of shorter duration than that following administration of Pethidine

SANDERS, Philadelphia

PNEUMOCOCCAL MENINGITIS TREATED WITH PENICILLIN H CAIRNS, E S DUTHRIE, W S LEWIN and H V SMITH, Lancet **1** 655 (May 20) 1944

The authors report on a series of 11 patients with pneumococcic meningitis treated with penicillin Of these, 3 were moribund and soon died, and the cases are not discussed here Of 8 patients receiving full treatment, 2 eventually died of diffuse purulent pachymeningitis and cerebral abscess Sodium and calcium salts of penicillin were used in daily doses averaging 3,000 to 4,000 units per injection but ranging from 10,000 to 85,000 units for total doses over periods of four to nine days

Penicillin was injected into the lateral ventricle or into the lumbar subarachnoid space or into both Cisternal puncture was not used either because there was free flow between the lumbar area and the ventricles or because, in 2 cases of block "it would not have helped" The drug was given in 3 cases by intramuscular injection as well, and "satisfactory blood levels were established"

Twenty-four hours after injection of 3,000 to 4,000 units the concentration of penicillin in the cerebrospinal fluid "was usually about 0 4 unit per cc—at least ten times that required to produce complete inhibition of the growth of a sensitive pneumococcus" The authors believe that the best way to achieve optimum concentration of penicillin throughout the cerebrospinal fluid is to give it simultaneously by the lumbar and the ventricular route

Reaction to injection was severe in only 1 case, in which a strong solution of sodium penicillin was used A mild reaction was "occasionally observed immediately after ventricular injection It consisted of patchy erythema of the skin of the trunk and limbs, often coming and going, generalised sweating, intermittent goose-skin, slight rise of pulse rate, and sometimes vomiting, the whole passing off in 10 to 20 minutes" The patient with the severe reaction showed the picture just described and then had a large bowel movement on the operating table She became drowsy, confused and hemiparetic (with residual palatal palsy and dysphagia for two months) Often patients complained of sacral and sciatic momentary pain during the course of lumbar injection

McCARTER, Boston

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

George D Gammon, M D, *Presiding*

Regular Meeting, March 23, 1945

Incidence, Clinical Characteristics and Restitution of War Injuries of Peripheral Nerves LIEUT MARTIN G NETSKY, Medical Corps, Army of the United States

The peripheral nerves were involved much more frequently in the second world war than in the first (18 vs 2 per cent) Injury to the radial nerve is commonest in civilian life, in military experience, injuries to the ulnar nerve are commonest (each 25 per cent), and next in frequency are injuries to the radial, median and peroneal nerves (each about 16 per cent) One fourth of all patients have injuries of more than one nerve Variations in the degree of motor overlap of the median and ulnar nerves are often puzzling The mechanism of the flexion position of the last two fingers in ulnar paralysis is still an unsolved problem Prevention of ulcers of the sole of the foot with tibial paralysis is an important problem in enabling patients to work A new method for the determination of the site of lesions of the brachial plexus was mentioned Sympathetic block has been found of diagnostic and therapeutic value in the treatment of burning pain The diagnosis of true causalgia has rarely been made Almost one third of peripheral nerve injuries recovered spontaneously

DISCUSSION

DR GEORGE D GAMMON Does Dr Netsky know any reason that causalgia is less common now than previously?

DR MARTIN G NETSKY There is no reason that I know of After the Civil War and World War I there were men who were reduced to emotional hulks, but such patients have not been seen at Cushing General Hospital

DR MICHAEL SCOTT Has Dr Netsky observed any results from nerve grafts?

DR MARTIN G NETSKY Yes, nerve grafting has been done at Cushing General Hospital It has been employed in a comparatively small number of cases, and for that reason I omitted mentioning it The results on the whole have not been successful In 2 of a small number of cases signs of regeneration were shown In the majority of cases the condition has not improved, and the problem is yet to be solved

DR JOSEPH C YASKIN I wonder whether Dr Netsky could inform us regarding the interruption or compression of nerves after operation Has anything new been learned since 1917-1919 in evaluating the anatomic changes of injured nerves prior to operation? In civilian practice this subject has been, and still is, a major question extremely difficult to answer It is true that the surgeon operates, but the clinical neurologist often has to determine the advisability of surgical intervention

DR MARTIN G NETSKY Handling depends on the site of injury With large gaps the ends are approximated when it is anatomically possible, as in the ulnar nerve Results with transposition of the ulnar nerve in cases of acute flexion of the arm have been fairly good In some cases, as in those of lesions of the median nerve in the palm, the procedure is not possible, and grafting is the only resort In a few cases bone shortening has been done

In answer to Dr Yaskin's question I think there are no new developments in preoperative estimation of the anatomic state of the nerve

COMDR WILLIAM GERMAN (MC), U S N R I do not believe that any great advance has been made since World War I

Surgeons have learned to use fine steel and some other forms of suturing material, such as a cobweb-like substance called tantalum I should be interested to hear what Dr Netsky and Dr Lewey have to say about these materials

Plasma glue is being used, of course, and its proponents will have to speak for it The chief problem now is the same as it was in the first world war—the approximation of the nerve ends This may necessitate the shortening of the extremity by bone sections Many times it means transposition and suturing of the nerve ends, with avoidance of the use of grafts whenever possible

Management of War Injuries of Peripheral Nerves MAJOR F H LEWEY, Medical Corps, Army of the United States

I am strongly in favor of the closest possible cooperation of neurologist and neurosurgeon, although the present setup in the Army may require an administrative separation All patients, whether "neurologic" or "neurosurgical," are admitted to the neurologic section, where they are examined and their cases completely worked up within one week They are presented to a combined conference of the neurologic, neurosurgical, orthopedic, medical and general and plastic surgical sections This conference has proved stimulating to all sections, and a great time saver to patients and medical officers alike In the neurologic examination, those methods are favored which give a permanent and numerical record, permitting comparison of objective data on the return of muscle power and of touch and pain sensitivity None of the methods of electrical examination so far available has given useful information on the actual condition of a nerve (bruise functional or anatomic interruption) Patients who require neurosurgical treatment are transferred to the neurosurgical section for operation and returned to the neurologic section for further observation, after-treatment and disposition New methods have been devised to shorten the time of mobilization of "frozen joints" ("joint bulldozer") and of waiting for the success of nerve sutures (action currents across the suture line) and for the final result (extended work furlough)

DISCUSSION

DR JOSEPH C YASKIN It appears that technical preoperative determination of anatomic interpretation of the nerve has not advanced since World War I

Dr Lewey lays less stress on the electrical studies which received so much attention, especially in Frank's school, in 1917 and 1919 Are Dr Lewey's procedures applicable in all cases except in those in which operation has been performed? Is there a closed method of evaluating the syndrome of regeneration? In other words, is there a way of telling the condition of the nerve without operation? Is the rate of recovery after operation considerable, and are there failures?

Lastly, Dr Lewey's anticipation of the care of these patients from the industrial standpoint is very wise, it is a view previously neglected

DR CHARLES RUPP Is Dr Lewey able to give any data on the average time required for function to return after compression neuritis? What is the maximum period before spontaneous improvement has been noted?

George D Gammon, M D, *Presiding*

Regular Meeting, April 27, 1945

Nontuberculous Meningitis in Children Report on Ninety-Five Cases DR J ALBRIGHT JONES, Swarthmore, Pa

During the six year period from 1939 to 1944, inclusive, 146 children with nontuberculous meningitis were admitted to the Children's Hospital of Philadelphia and to the pediatric ward of the Philadelphia General Hospital

Of the 146 patients, 96 had meningococcic meningitis, 20, influenzal meningitis, 19, pneumococcic meningitis, and 9, streptococcic meningitis (2 children with meningitis due to Escherichia coli were not included because they have been reported on before this society by Dr Gammon)

The mortality percentages were as follows meningococcic meningitis, 93, influenzal meningitis, 65, pneumococcic meningitis, 95, and streptococcic meningitis, 55

Of the patients with meningococcic type, the records showed petechiae in 20 per cent, the meningococcus was reported in blood cultures in 19 per cent, in spinal fluid cultures in 64 per cent and in smears of the spinal fluid in 73 per cent

Among the 14 patients with influenzal meningitis at the Children's Hospital there were 9 deaths (mortality, 64 per cent) Among the 6 patients at the Philadelphia General Hospital there were 2 deaths (mortality, 40 per cent) Of the 20 patients, Hemophilus influenzae was found in smears of the spinal fluid in 80 per cent, in spinal fluid cultures in 70 per cent and in blood cultures in 30 per cent

Laboratory data on the 9 patients with streptococcic meningitis were as follows Streptococci were found in spinal fluid smears in 62 per cent, in spinal fluid cultures in 100 per cent and in blood cultures in 25 per cent (2 patients did not have blood cultures made)

All but 1 of the 18 children with pneumococcic meningitis died (94 per cent mortality) Pneumococci were found in spinal fluid smears in 88 per cent, in spinal fluid cultures in 94 per cent and in blood cultures in 22 per cent

With the exception of the patients with meningococcic meningitis at Philadelphia General Hospital in 1944 who were treated with sulfamerazine, not enough patients were treated with any single drug to warrant conclusions regarding the efficacy of a single type of therapy However, from the reports cited, it seems certain that at present the following statements can be safely made Sulfadiazine, sulfamerazine and penicillin are all effective agents in the treatment of meningococcic meningitis Serum is rarely beneficial Sulfadiazine and anti-influenzal rabbit serum form the best combination for treating infections with type B H influenzae Sulfadiazine or sulfamerazine with penicillin probably forms the most effectual combination in the treatment of pneumococcic meningitis Surgical drainage is worthy of more study The use of penicillin and a sulfonamide compound for this type of meningitis has been recently reported as an improved therapeutic measure Streptococcic meningitis should be treated with the same combination as is used for pneumococcic meningitis Foci of infection in pneumococcic and streptococcic meningitis must be thoroughly cleaned up

Early diagnosis must be stressed Parents can help by being "meningitis conscious" during epidemics of meningococcic meningitis More thorough laboratory work in identification of the causative organism is needed Much can be accomplished by the intern who makes the first spinal puncture

Further consideration of surgical drainage in cases of pneumococcic meningitis is needed Adequate treatment of foci of infection is necessary in treatment of influenzal streptococcic and pneumococcic meningitis

Every hospital should have a detailed plan of management of all cases of meningitis which the intern can follow This would undoubtedly reduce the mortality figures

DISCUSSION

DR JOSEPH C YASKIN A striking feature of Dr Jones's report is that with chemotherapy so many patients with influenzal infections recover It would be interesting to hear what specific treatment was used for influenzal meningitis Another point of interest in his study is the high mortality in pneumococcic meningitis I was under the impression that the mortality was lower I should like to ask Dr Jones how often it was necessary to do a mastoidectomy or other gross surgical procedures after the acute stage of the meningitis treated with a sulfonamide compound

DR J ALBRIGHT JONES, Swarthmore, Pa I cannot answer that question accurately, because there is no way in which I could get a good follow-up report on these patients I hoped that Dr Gammon would be here tonight, for he sees most of the patients, or a large percentage of them, after they leave Children's Hospital, and he could give us an idea as to the number of complications I should say roughly that few patients with meningococcic meningitis have any complications In the early days, when treatment was not so good as it is now, probably 1 patient out of 10 had a complication of some kind There was not 1 case of "chronic meningitis" in this group Later, some patients reported having headaches or other complications or symptoms associated with more activity at home Small children cannot tell one much When, later, they begin to walk, they may have difficulty with locomotion Our records are not revealing with respect to such complications of convalescence I omitted the question of complications on purpose, because the patients are so seldom seen by a good neurologist Most of them did very well, with no complications, so there was no routine examination before discharge

There is no doubt that the plan of therapy Dr H E Alexander had been using with influenzal meningitis has given the best mortality figures Her mortality rate was about 20 per cent of 87 cases, which is extremely good

In cases of pneumococcic and streptococcic meningitis, with which there is usually air-associated infection of the middle ear, mastoidectomy is fairly common but I cannot state exactly how often it is necessary Therapy has improved a great deal, and there have been fewer cases of infection of the mastoid in recent years The whole picture changes as one goes through the records For example at Philadelphia General Hospital this year there have been 3 patients with pneumococcic meningitis, all of whom recovered Only 1 patient recovered in the period from 1938 to 1945

Paroxysmal Autonomic Crises in Postencephalitic State Report of a Case DR CHARLES I OLLER

This paper was published in full, with discussion, in the April 1946 issue of the ARCHIVES, page 388

Arteriovenous Aneurysm of Great Cerebral Vein and Arteries of Circle of Willis DR BERNARD J ALPERS and DR FRANCIS M FORSTER

This paper was published in full in the September 1945 issue of the ARCHIVES page 181

DISCUSSION

DR CHARLES RUPP I wonder whether Dr Alpers has any theories as to the cause of this anomaly

DR BERNARD J ALPERS Not only do I not have any theories, I do not know how the condition would be identified if it were met again It is obviously a congenital disorder

DR FRANCIS M FORSTER Streeter's observations indicate that the great cerebral vein develops some time between the 50 and the 60 mm stage Thyng described the appearance of the posterior cerebral artery at the 17 8 mm stage It is difficult to understand the development of an arteriovenous aneurysm such as this with such a wide difference in the stages of appearance of its various components

DR MILTON K MEYERS I should like to ask Dr Alpers how long this boy had the hydrocephalus

DR J RUDOLPH JAEGER Dr Alpers' most interesting case of multiple arteriovenous communications of the cerebral vessels is amazingly similar to the one I reported by title at the Sixty-Third Annual Meeting of the American Neurological Association in June 1937 (*Tr Am Neurol A* **63** 173, 1937)

My patient was 4 years old at the time of death and had suffered from many attacks of severe nasal hemorrhage, requiring numerous transfusions and nasal packings The only objective sign of an intracranial lesion was moderate hydrocephalus Auscultation over the carotid arteries disclosed loud bruits, and palpation revealed thrills over these vessels An intracranial arteriovenous communication was suspected Injection of 20 per cent sodium iodide into the left internal carotid artery disclosed that this vessel was so enlarged and tortuous as to be completely looped in the neck The contrast medium was so diluted, however, by the huge volume of blood passing into the cranial cavity that the details of the anastomosis could not be visualized Several months later death followed a violent convulsion

Necropsy disclosed dilated ventricles with probable obstruction of the aqueduct by a huge aneurysm of the straight sinus Numerous branches of the posterior and middle cerebral arteries had direct communications with many of the central veins of the brain, principally those draining into the straight sinus Strangely, in both cases examination showed no obvious communications in the anterior cerebral arteries, although it is probable that tiny ones existed The whole intracranial venous system, including the straight, transverse and sagittal sinuses, were greatly dilated probably due to arterial pressure inside the venous channels, although this could well have been a part of the congenital malformations

This case illustrates the fact that nature always repeats its mistakes, no matter how rare they may appear I well remember Dr Walter Dandy's comment after he had seen and studied the specimen in my case "Some day another case with precisely the same deformity will appear" Dr Alpers' presentation of his case fulfils this prediction

DR BERNARD J ALPERS The patient had had headaches since he was 6 years of age His hydrocephalus must have developed after the sutures were closed, for there was no indication of separation of the sutures and no cracked-pot signs were obtained on percussion The hydrocephalus probably developed simultaneously with the appearance of the headache

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PHILADELPHIA PSYCHIATRIC SOCIETY

O Spurgeon English, M D, *Presiding*

Regular Meeting, May 11, 1945

Function of the United States Naval Hospital COMDR JOHN M MCKINNEY (MC), U S N R

The neuropsychiatric casualty in point of numbers, in point of cost to the Government for future care and in point of rehabilitation and social readjustment is the major problem of military medicine and after the war will become one of the major problems of civilian psychiatry There are too many of these casualties to be taken care of by federal agencies like the Veterans Bureau Even if all the psychiatrists in the service were to be turned over to the Veterans Bureau, they could not do the job Most of these patients must be looked after by civilian agencies and civilian psychiatrists This is one of the reasons that we on the staff of the United States Naval Hospital here are anxious to present this program to the Philadelphia Psychiatric Society The neuropsychiatric casualties consist of the psychotic patients, who constitute 1 to 2 per cent of our total admissions, the patients with organic neurologic disorders, consisting mostly of head injuries and peripheral nerve injuries, the psychopathic personalities, the percentage of whom is about the same as that in civilian life, and not an inconsiderable number of patients who are not strictly psychiatric but are the so-called gold-brickers These men assume symptoms for the purpose of getting out of the service They are resentful, antagonistic and stubbornly determined to have their way They do not break the rules, and therefore one cannot punish them There is no treatment

that seems to have any effect They will not work, and if they are sent back to duty they report to sick bay the next day with their complaints and continue to do so until they get back on the sick list Although we may be convinced that they are consciously assuming their symptoms, we cannot prove it If the man says he has a headache or a backache which is incapacitating, it is impossible to prove that it does not exist There is only one thing left to do, and that is to get him out of the service on a medical discharge, which, unfortunately, gives him the same type of discharge as the other patients, but this is the best we can do in the circumstances

By far the greatest percentage of our patients falls into the group with what is known as combat fatigue, or war neurosis Typically these men, without an actual wound, collapse on the field of battle and are unable to carry on They either lose consciousness or become dazed and mute and are seized with violent shaking and tremor They frequently vomit They may go berserk, start shooting in every direction, begin running either toward or away from the enemy and have to be forcibly restrained Many men with this acute condition are returned to duty after a few days' treatment in a forward hospital Those with a more severe disorder are evacuated It has been my experience that once these patients are evacuated they seldom return to combat duty Through a series of hospitals, they gradually are transferred back to the states on the sick list and eventually come to such a hospital as this for disposition

Now, it is easy to serve as a disposition hospital It is easy to say that this man has been hospitalized for six or seven months, that his condition is not improved, that his symptoms are fixed, that he is of no further use to the service and that his discharge is recommended, but such a system turns out many men on the country who are nervously unsuited to hold a job They are turned out in such numbers that they cannot be adequately looked after by the Veterans Bureau or by the available psychiatrists in civilian life We feel that it is our duty to restore to usefulness every one of these men we possibly can, so that they can go back to limited duty or be discharged to civilian life With this in mind, we treat every patient who shows any possibility of improvement

In dealing with such a varied personnel we have found it necessary to adopt a number of technics The officers, by and large, do well with the psychiatric interview and with group psychotherapy Most enlisted men consider this treatment just so much "bunk," and it not only leaves them cold but annoys them We have made use, therefore, of every therapeutic means that we could think of and are still looking around for more We have used suggestion, hypnotism, narcosynthesis and persuasion We are not unaware of the coexistence of organic diseases in some of these patients, and we make full use of our consultation service with this in mind Occupational therapy, in all its phases, has been helpful, and this means of treatment is improving and becoming more efficient as time goes on Each man capable of doing so spends two hours a day on the athletic field Recently, there has become available to us the rehabilitation work program, whereby jobs in local civilian plants are obtained for these patients while they are still on the sick list This work is either in the nature of an apprenticeship or along the lines for which the patient's education and former occupation fit him These patients have all been seen by a Board of Medical Survey, and their separation from the service has been advised Even though this program has been in use only a short time, its results are most gratifying These men have their confidence restored, they know they can hold a job, they sleep well without medication, their appetites improve, and their symptoms largely disappear After a period of work, in which we are assured that the patient can go out and face the world and hold a job, he is given a discharge

The Psychotic Patient LIEUT COMDR JAMES C ROBERTSON (MC), U S N R

The psychotic patients represent a relatively small portion of psychiatric patients seen at this facility and constitute approximately 1 3 per cent of the total psychiatric

monthly census This figure applies to the psychotic patients who require further institutional care and does not account for the very few such patients who recover to the extent that they may be released from this hospital

Dementia precox is the most common psychosis, as might be expected Reactive types of depression and varying degrees of depression accompanying severe war neuroses are observed fairly frequently Only an occasional patient with manic-depressive psychosis is seen, and paranoid conditions have been extremely rare Patients with organic psychoses are relatively few, with only an occasional case of psychosis with cerebral arteriosclerosis, toxic psychosis or the psychosis of dementia paralytica

Patients with mild degrees of depression associated with a psychoneurosis and those with personality disorders of the emotionally unstable, inadequate and constitutional psychopathic inferiority types are often admitted to the psychotic ward, frequently after self infliction of wounds of a superficial character Many such acts occur during a "panic" reaction and are most often in the nature of a suicidal gesture, consciously motivated, in an effort to escape the unpleasant situation relative to being in the service or in being confined in the brig These wounds usually consist of several superficial scratches and often occur on one or both wrists There is a history of the patient's insuring that his behavior was observed before, during or immediately after such an act was committed The depth of the wound is evidence of the seriousness or lack of seriousness of the attempt, and wounds of more than superficial penetration of the skin are considered evidence of some degree of depression or of a psychosis The majority of these basic personality disorders, with or without some degree of associated depression, clear up rapidly with hospitalization, sedation and reassurance As to the disposition of the patient, which constitutes separation from the service The man who will go to the extent of inflicting a wound on himself, even though it is trivial and used entirely as a means of escape, is considered to have too poorly an integrated personality to adjust to, or to make any satisfactory or dependable contribution to, the service and is better disposed of at the earliest possible moment

Specialized treatments, such as electric, insulin and metrazol shock, are not carried out on psychotic patients in this hospital The problem here is for the most part one of disposition, and all men with actual psychoses are transferred to St Elizabeths Hospital, Washington, D C, for their further treatment and final disposition This method of handling the psychotic patients is uniform throughout Naval hospitals Patients are retained in this hospital only long enough for complete studies, establishment of a diagnosis and estimation of the probable future duration of the psychosis Those patients who reveal indications of improvement or who have a relatively mild upset and show promise of improvement in a short time without special forms of treatment may be held for several weeks and eventually be discharged from the hospital as recovered

In addition to the aforementioned patients, many persons with constitutional psychopathic inferiority state, in a prisoner status and awaiting disciplinary action or serving sentence, are seen for evaluation and recommendations as to their future disposition Discharge from the service is usually recommended An opinion is necessary as to their mental competence and as to whether disciplinary action and confinement would have a deleterious effect on the patient's mental or physical health

Neuropsychiatric Casualties Resulting from Exposure to Atmospheric Blast LIEUT PEARCE BAILEY (MC), U S N R

At the beginning of World War I the term "shell shock" was used to describe an unconscious soldier who was found lying uninjured near an exploded shell By the end of the war this newly coined term had been expanded to include all forms of war neuroses In World War II attention became centered on the effects of atmospheric blast, largely because of the indiscriminate bombings of dense civilian populations The term "blast shock" or "blast concussion," was given to the

condition of the unconscious, uninjured soldier who was discovered in the vicinity of a previous explosion

Whether the effect of a blast in itself can produce cerebral concussion is still controversial The animal experiments of Denny-Brown and Russell tend to deny that it can The practical clinical implication of this conclusion is that persons suspected of having a concussion can be immediately transferred to a psychoneurotic classification if it can be demonstrated that their exposure to blast was not followed by secondary impact with a solid surface

From the standpoint of Naval neuropsychiatry, the nuclear problem in relation to alleged blast experience is the differentiation between a possible resultant post-concussional syndrome and a neurotic complex For it is on the basis of this differentiation that therapy, prognosis and ultimate disposition depend As a consequence of explosions, one does see post-traumatic syndromes, purely neurotic manifestations and combinations of the two in varying degrees

Among several patients observed in this hospital during the last six months, there was only 1 with what we interpreted as a pure concussion About one eighth of the patients disclosed organic signs with superimposed neurotic manifestations, the former predominating An equal number showed a combined picture with neurotic elements predominating, and three fourths of the men appeared to have pure neurotic syndromes Thus, it appears that the commonest disability is preeminently psychologic The most prevalent neurotic reaction was that of anxiety There was occasional evidence of hysterical fragments, but no obsessive-compulsive states were observed

In an over-all study of the practical aspects of blast concussion, we believe that a careful evaluation of both organic and psychologic factors is essential An inclination to declare the condition in any given case as either organic or functional without careful assessment of all values should be discouraged, tempting as it might be For exposure to blast can cause cerebral concussion either by itself or by hurling the skull against a rigid resistance But it also can produce pain, which includes a threat to the integrity of the head—probably the most highly prized organ of the body It can act as a precipitant of a dormant fatigue reaction or it can activate a previously sublimated neurotic conflict

In the evaluation of these patients we make a careful search for a history of evidence of surface injury to the head Prolonged unconsciousness, mental changes, such as confusion, disorientation, retardation and distinct alterations of personality, bloody spinal fluid, abnormal neurologic signs (even though evanescent), focal and general abnormal electroencephalographic phenomena—all are characteristic of altered cerebral economy Decreased tolerance to alcohol steady improvement in symptoms and a desire to return to duty also suggest an organic cause A history of dizziness, increased by postural changes, or inability to concentrate has less diagnostic value The former is easily elicited by suggestion, the latter is just as common to an anxiety state as to a postconcussional syndrome

We endeavor not to overlook the possibility of a subdural hematoma or effusion These lesions frequently show no focal neurologic signs, and papilledema may not be present until late, if at all A history of head trauma followed by an alternating or shifting state of consciousness with a downhill course should arouse suspicion Often pneumoencephalographic examination or exploratory trephination is necessary to establish the diagnosis

From our observations, an inconstant course, extreme variability of symptoms, dramatization and attitudinization egocentricity and, especially unwillingness to return to duty favor a psychogenic interpretation Autonomic instability is common to both types but is usually more erratic and intense in anxiety states Generalized constriction of the visual fields, diminution of corneal and gag reflexes and a "cloak" of hypalgesia (Foster Kennedy) suggest conversion phenomena We have found intravenous injection of sodium amytal or pentothal of considerable diagnostic aid Patients with combat fatigue experience an intense abreaction of battle scenes, psychoneurotic patients are apt to be resistant and argumentative, whereas patients with postconcussional states tend to become confused Finally,

the use of psychometric tests, particularly those of Rorschach and of the Hartford Retreat, has been helpful in corroborating other signs of transitory mental slowing, which is frequently characteristic of a postconcussional state

As to therapy, we treat the patients with predominantly organic disturbances by means of a program of rest, assurance and occupational therapy To patients with postconcussional states who have additional mild symptoms of combat fatigue we offer narcosynthesis and a series of psychiatric interviews The patients manifesting more chronic personality disturbances are sent for rehabilitation to a convalescent annex of a United States Naval hospital On the whole the results have been encouraging

Group Therapy of Combat Fatigue LIEUT MANUEL M PEARSON (MC), U S N R

Group therapy, largely because there are too many patients and too few psychiatrists, has become an accepted form of psychotherapy in the military services The method consists of a short talk on a specific subject followed by an open and free discussion The essential characteristics of each talk should be brevity, simplicity of language, many examples and illustrations of essential points and appropriate questions that are stimulating and thereby control the session

The group therapy is supplemented by an active daily program consisting of occupational therapy, physical reconditioning and educational measures, such as audiovisual aids in the form of training films, illustrated lectures and short skits All the accepted methods of individual therapy, such as catharsis, desensitization and reeducation, operate in group therapy In addition, group identification takes place, attacking specifically one of the chief causes of combat fatigue, that is, breakdown of morale

In group therapy at the convalescent annex of a United States Naval hospital, an attempt is made to attack the two common denominators of combat fatigue (1) anxiety, mainly expressed by uncontrollable aggressiveness and bodily symptoms, and (2) depression

From 45 to 50 per cent of the patients treated in this highly selected group have been returned to duty, mainly to a noncombatant status

A chart illustrating the entire program for treatment of patients with combat fatigue at this annex was presented

Combat Fatigue LIEUT COMDR JOSEPH HUGHES (MC), U S N R

A group of Naval men suffering from combat fatigue was presented These men were typical cases of combat fatigue as seen in persons who had stable personalities prior to combat Patients of this type respond favorably to treatment

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CINCINNATI SOCIETY OF NEUROLOGY AND PSYCHIATRY

Charles D Aring, M D, *President, in the Chair*

Regular Meeting, Oct 9, 1945

The Clinical Application of Electroencephalography DR GEORGE L ENGEL

Since the introduction of the electroencephalograph, some twelve years ago, an enormous amount of data, mostly empiric, has been accumulated in the literature It seems timely to consider some of the theoretic aspects of electroencephalography and to attempt to derive from them a basis for its application to problems of clinical medicine

In the final analysis, the electrical activity of the cortex derives from the activity of the individual neurons, the energy for which arises from the intrinsic metabolic activity of the cell (Gerard, R W Factors Influencing Brain Potentials, *Tr Am Neurol A* **62**·55, 1936) Neuronal potentials may be expected to be

influenced by the following factors (1) changes in cell metabolism, (2) changes in the electrical properties of the cell membrane, (3) the character of the surrounding fluid medium and (4) influent electrical impulses both independent of and along neural pathways Changes in rate, form and within limits, amplitude may be interpreted in part in terms of the individual neuron beat

However, to account for the rhythmicity and regularity of the electroencephalographic record, some mechanism of synchronizing the individual neuron beats must be assumed For this a theoretic pace-making system has been postulated, possibly cells the electrical activity of which set other cells off The more efficient the synchronizing process, the more regular will the record be Synchrony might then be influenced by (1) the metabolic activity of the pacemaker cells, (2) functional or structural disruption of pacemaker systems and (3) the effect of influent electrical impulses

A third important factor has to do with the physical properties of oscillating systems (Dawson, G D, and Walter W G Scope and Limitations of Visual and Automatic Analysis of the Electroencephalogram, *J Neurol, Neurosurg & Psychiat* 7 119, 1944) With a mixture of different components, important considerations in determining the final complex are (1) whether the sinusoidal oscillations belong to a harmonic series, (2) to what degree the various components are in phase, (3) whether the amplitude fluctuates rhythmically (modulation) and (4) the algebraic sum of the amplitudes These considerations are obviously of most importance in circumstances in which there is a mixture of electrically active tissue components or discharging foci

The normal electroencephalogram has been arrived at by a statistical approach and there is now fairly general agreement as to its limits It is influenced by age, by alterations in attention, by reduction in blood sugar and oxygen tension and by numerous drugs that affect cortical activity In general, hypoxia and hypoglycemia produce progressive slowing and irregularity, and the degree of slowing correlates with the degree of reduction in consciousness Voluntary hyperventilation produces some degree of slowing in all persons, to a more striking degree in younger subjects, but there is great individual variation In any one subject the amount of slowing during hyperventilation is increased by (1) lowering blood sugar, (2) lowering oxygen tension of the inspired air and (3) assuming the erect posture Slowing is always accompanied with some reduction in the level of consciousness

The abnormal electroencephalogram may be characterized by too slow potentials or too fast potentials or a mixture of the two These abnormal frequencies may be nonparoxysmal, being continuous in respect to time, or they may be paroxysmal, intruding as it were into an otherwise normal record In either instance the abnormal frequencies may be generalized or focal

The nonparoxysmal type of abnormal record is the result basically of disturbances in cerebral metabolism The prototype of these disturbances is delirium, in which the degree and character of change in the electroencephalogram are more or less independent of the etiologic factor, whether it be anoxia, hypoglycemia, fever, drugs or intracranial disease, but is dependent on (1) the intensity of action of the noxious factor, (2) the acuteness of its action, (3) the duration of its action (4) the reversibility of its action, (5) the premorbid status of the central nervous system and (6) the relative proportion of uninjured, damaged and destroyed neurons The more acute and intense the process and the larger the proportion of damaged cells, the greater are the changes likely to be in the direction of slowing and irregularity and the better is the correlation with level of consciousness The more gradual or chronic the process and the fewer the cells actually damaged at any one time—though there may be many destroyed cells—the less striking are the electroencephalographic changes likely to be, in spite of pronounced disturbances in awareness These data are based on studies of cases of acute and chronic delirium, dementia, various types of diffuse organic disease of the brain and syncope

With nonparoxysmal abnormalities of a focal character the same principles hold true, with one important modifying factor, namely, the proximity of the lesion to the nearest electrode and the amount of interposed normal brain tissue Studies of patients with cerebral vascular lesions—softening, hemorrhage, vasospasm, subdural hematoma—or with cerebral abscess or cerebral tumor provide the data for these conclusions

The paroxysmal abnormalities are characteristic of epilepsy The basis of the paroxysmal activity still remains obscure, although it is convenient to think of it as a discharge phenomenon, and as such it is basically different from the nonparoxysmal type of abnormality Sometimes, however, the discharges may be so frequent or so prolonged as to render differentiations from nonparoxysmal abnormality difficult In general, our observations amply confirm the data presented in the numerous publications of the Gibbses, Lennox, Jasper, Williams and others We would emphasize one point, however, namely, the negative diagnostic value of hyperventilation unless a wave and spike pattern is provoked

In our experience, the electroencephalogram obtained in cases of neuroses, psychoses, psychopathies, alcoholism and behavior problems of childhood is not essentially different from the accepted range of normal patterns when they are properly corrected for age and when epilepsy, organic disease of the brain and the active effects of such factors as trauma, alcohol and drugs are excluded

This paper was published in full in the March 1946 issue of the *Cincinnati Journal of Medicine,* page 151

DISCUSSION

DR MAURICE LEVINE Have there been any electroencephalographic studies of normal or neurotic subjects in a state of anger or temper or other acute emotion? In the material Dr Engel mentioned, the patients were in a relatively calm state, were they not?

DR GEORGE L ENGEL Most of the patients reported on in the literature were not watched closely or adequately during the period of study I know of no specific studies in which that point was investigated It would be technically very difficult to get records on patients during a display of anger

DR MILTON ROSENBAUM In the group of epileptic patients about 40 per cent had a paroxysmal disorder and 20 per cent had a nonparoxysmal interseizure disorder I gathered from Dr Engel's paper that unless there was a paroxysmal disorder he would not make the diagnosis of epilepsy from the electroencephalographic record On the other hand, it seems to me one has to take into consideration the clinical side of the picture In other words, if a patient had some sort of spell and a disturbance appeared in the electroencephalogram, either fast or slow nonparoxysmal activity, with no neurologic signs, would Dr Engel not be inclined to consider that indicative or confirmatory of epilepsy?

DR GEORGE L ENGEL Yes, that is why I am sometimes insistent about not reporting on an electroencephalogram until I get clinical information If I read a record with wave and spike activity, I am sometimes willing to report it without seeing the protocol The more precise and accurate the clinical information, the more reliable will be the electroencephalographic interpretation However, I rarely use the phrase "diagnostic of" in my reports, "suggestive of" or "consistent with" is the more usual expression I usually am still cautious, however, because the requisitions are sometimes hurriedly written and not always accurate For example, I have sometimes obtained generalized nonparoxysmal, abnormal records from ward patients and have later found that the patient was delirious at the time the record was taken, even though no mention of this was made on the requisition But I believe that in general Dr Rosenbaum's statement is correct The more complete the information is at the time of the tracing, the more reliable is the interpretation

DR MILTON ROSENBAUM I think that clinical judgment probably means more than the interpretation of the electroencephalogram Dr Engel did not comment on the 14 per cent of so-called normal people who have abnormal records

DR GEORGE L ENGEL I did not comment on the 14 per cent who show diffusely moderate slow or fast activity because I am still not sure whether I should consider as abnormal all the records that Gibbs does I believe my criteria are a little less rigid Further, I am still not sure that they all mean epilepsy, particularly those with nonparoxysmal activity

DR MILTON ROSENBAUM That is important, it may be that one does not know enough to decide One of the most interesting contributions made by Gibbs and his group is the idea that these apparently normal persons with abnormal activity are carriers of convulsive disturbance Much can be built up with this theory in mind, and I wonder what Dr Engel's own feeling is

DR GEORGE L ENGEL I think the idea is worth keeping in mind, but I don't think that it has as yet been proved that these people are "carriers," although the data on inheritance are certainly suggestive

DR I ARTHUR MIRSKY Dr Engel has emphasized the metabolic aspects of the electroencephalogram and has pointed out that the frequency tends to increase with administration of dextrose to normal persons Given a patient with delirium who has slow activity, would the activity increase when carbohydrate is administered, as it does in hypoglycemic patients? It seems to me that all the mechanisms that cause slowing of the waves seem, in the final analysis, to be associated with depletion of glucose in the brain

DR GEORGE L ENGEL My associates and I have not studied the effect of intravenous administration of dextrose on a sufficient number of delirious patients to know whether a slight effect may not be produced in the absence of hypoglycemia The only group of patients that we have studied carefully is one with Addison's disease When these patients have hypoglycemia, the administration of dextrose has a specific effect When the blood sugar is normal, the intravenous administration of dextrose has no effect on the electroencephalogram of patients treated with desoxycorticosterone acetate but does have an effect on the electroencephalogram of patients receiving large quantities of adrenal cortex extract The few other delirious patients we have studied show no particular response, but this point has not been investigated carefully enough

I do not believe the data available support the assumption that slow waves are related primarily to depletion of glucose I suspect that if the respiratory cycle is interrupted at any stage slow waves might result The barbiturates, for example, interrupt the cycle at the lactic acid–dehydrogenase stage, and high voltage, slow waves result I do not believe that administration of dextrose will affect this abnormality in the electroencephalogram

DR PHILIP PIKER Clinically, in patients with certain disturbances of lowered awareness the intravenous administration of dextrose seems to have had a beneficial effect, for example, in the aged in the surgical wards who have delirium as a complication of trauma (usually fracture), or perhaps as a result of too much sedation Patients with barbiturate intoxication often show some response to administration of dextrose in that their level of awareness becomes higher, an observation which would fit in with this notion, too

DR GEORGE L ENGEL I do not believe that these clinical observations have been adequately controlled with respect to the multiplicity of factors involved However, they ought to be tested in the laboratory

DR I ARTHUR MIRSKY What happens in the case of diabetic patients with hyperglycemia but without acidosis?

DR GEORGE L ENGEL We have not studied such patients I should point out here that oxygen will affect the electroencephalogram in patients without anoxemia The patient with cardiac disease whose record I showed, gave a striking electroencephalographic response to the administration of oxygen, yet the arterial oxygen saturation prior to therapy was 94 per cent We have studied a number of patients since and have found that inhalation of 100 per cent oxygen does improve the electroencephalogram even though the patient does not have anoxemia This is

true in cases of cholemia, uremia and heart failure, so we know a bit more about that than we do about the effect of dextrose

DR CHARLES D ARING It is interesting that the aged epileptic patient tends to have a normal electroencephalogram This correlates with what is known about the diminution of seizures with increasing age, an effect which has been attributed to stiffening It has been supposed that the aging muscles discouraged the exteriorization of the cerebral abnormality Have any electroencephalographic studies been made in seriatum with increasing age? Have such patients been studied over a number of years?

DR GEORGE L ENGEL I believe such studies have been initiated, but I have never seen any reports In our experience with children with seizures the records tend to become less abnormal, particularly after the age of 14, but how much is due to decrease in the epileptic factor, how much to maturation and how much to therapy I do not know It would be difficult to carry out such an experiment, for one would have to get records practically daily in order to control the day to day or week to week variation

DR EDGAR L BRAUNLIN, Dayton, Ohio What effect would the water-pitressin test have on the electroencephalogram?

DR GEORGE L ENGEL So far as I know such a test has not been made We tried it once, the patient became delirious before she had a fit The electroencephalogram showed diffuse abnormality I do not know how often that occurs

DR A WIKLER, Lexington, Ky My colleagues and I at the United States Public Health Service Hospital, Lexington, Ky, have studied the effects of pitressin hydration on the electroencephalograms of drug addicts None of the subjects was known to have epilepsy In about one-half the subjects bursts of slow waves were produced by pitressin hydration Most of those who exhibited paroxysmal slow activity in the record also showed a shift to the slow side of the frequency spectrum There were a few who showed a shift to the slow side on the spectrum but no paroxysmal slow activity and vice versa We have not yet tried this test on epileptic patients, but we plan to

DR JOHN ROMANO How many of the subjects had fits?

DR A WIKLER, Lexington, Ky None of them had fits One patient was referred to us because of periodic disturbances in behavior He was considered psychopathic, but it was desired to rule out an epileptic variant We found nothing abnormal in his routine electroencephalogram but suggested that the pitressin hydration test be made Such studies were carried out, and a shift to the slow side and paroxysmal slow activity were observed, but abnormal behavior was not produced Still we were not sure whether these changes were to be considered normal or not, so we made further studies Now we have the data Of course, we still do not know whether these changes occur in persons not addicted to drugs, since we have no normal controls Most of our drug addicts are classified under the head of psychoneurosis or psychopathic personality

DR GEORGE L ENGEL Did Dr Wikler study the level of awareness?

DR A WIKLER, Lexington, Ky There was no gross impairment of the level of awareness Some of the patients who showed paroxysmal slow activity or a shift in the frequency spectrum were uncomfortable, restless and anxious Yet they exhibited paroxysmal slow waves They did not show any evidence of lowering of the level of consciousness

DR GEORGE L ENGEL My experience in the study of delirium would lead me to suspect that some of these patients described as uncomfortable, restless and anxious would show reduction in awareness if they were tested more precisely I believe that Dr Wikler's demonstration of paroxysmal activity during pitressin hydration is of great significance

Book Reviews

A Future for Preventive Medicine By Edward J Stieglitz, M D, F A C P Price, $1 Pp 68 New York The Commonwealth Fund, 1945

In the third member of the series of monographs sponsored by the New York Academy of Medicine, Committee on Medicine and the Changing Order, Stieglitz writes a forceful and provocative essay on the changing emphases on preventive medicine His view of the field is not confined to the activities of health agencies but reaches far into education, research and all the health-building efforts which he terms "constructive medicine"

The main theme of the essay is the need for changing the disproportionate attention, in the present modes of approach, given to the wholesale preventive measures directed against environmental threats Individualized protection is needed at all ages, whereas at present its use is practically confined to obstetrics and pediatrics More than one third of the book is taken up by a review, with charts, of the well known changes in vital statistics over the last forty years, the aging of the population due to the successful exploitation of knowledge of bacterial diseases chiefly affecting early life Emphasis is laid on the increasing burden of the chronic diseases of middle life, leading to the extensive invalidism of the 60's and 70's

In announcing his program for preventive medicine, Stieglitz, of course, advocated a completion of the mass methods of minimizing health hazards Extension and coordination of preventive activities by agencies, public and private, is essential He reminds the reader that the United States is the only senior nation which has no secretary of health but gives cabinet rank to the Postmaster General! But coordination, he says, must be achieved cooperatively, for "a superimposed, centralized, directing authority, such as implied in the Wagner-Murray Bill is almost certain to destroy initiative, suppress imagination and retard progress" A plea is made for a generous expansion of research, supported by tax money, into the causes of degenerative disease He calls on physicians to come out of their offices and laboratories to lead the fight on ignorance In schools and colleges, on newspaper and radio staffs, they must see that the public has accurate and not oversimplified information on biologic and health matters

But his greatest hope for the extension of health, especially in middle and later life, lies in the private, or retail, approach Fundamental to it is the acceptance of the idea that health is a personal responsibility, a privilege which cannot be granted by any governmental system but earned by only the individual for himself Stieglitz foresees "well adult clinics" as common as well baby clinics In office or clinic the patient would receive a "health inventory" and guidance on living habits based on tests of functional capacities

The author is a gerontologist, mainly concerned with the postponement and control of degenerative disease In his somewhat austere view of individual preventive medicine, he hardly seems aware of the newer approach which views the individual as inseparable from a family or community setting "Patients have families"—so do well people The potential development of child guidance is hardly hinted at, and preventive psychiatry in the preschool years is not mentioned Nor is marriage counseling noticed

The sterility of the periodic health examination movement has been due partly to the blindness of its advocates to social and emotional reasons for poor health Therefore attention might well have been called to the Peckham Health Center, in London, where families had the benefit not only of medical guidance but also of the facilities which made healthy living possible

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OCCURRENCE OF MULTIPLE NEURITIS IN CASES OF CUTANEOUS DIPHTHERIA

MAJOR HERBERT S GASKILL
AND
CAPTAIN MILTON KORB †
MEDICAL CORPS, ARMY OF THE UNITED STATES

CUTANEOUS diphtheria is rarely seen in the temperate zone, but it is a common cause of disability among soldiers serving in the tropics [1] Abrasions, blisters, insect bites, gunshot wounds and dermatophytic fissures, to mention only a few of the common lesions of the skin, are frequently secondarily infected with virulent Corynebacterium diphtheriae These infections develop into the chronic ulcers of cutaneous diphtheria, which have been called variously desert sores, septic sores, barcoo rot and veldt sores

In the fighting around Myitkyina during the North Burma campaign a small epidemic of cutaneous diphtheria occurred among American soldiers One hundred and forty cases of this condition were studied at the Twentieth General Hospital In 61, or 43 per cent, of this group multiple neuritis developed as a complication The purpose of this report is to analyze and record the observations in these cases of neuritis Articles covering the dermatologic, bacteriologic and cardiac aspects of this series are to be reported by Livingood [2] and Kay [3] and their associates

These 140 cases of cutaneous diphtheria were divided into two groups—A and B In group A, consisting of 109 cases, the patients were admitted directly to this hospital shortly after their diphtheritic

† Captain Korb died Dec 29, 1945

1 (*a*) Wilson, S A K Neurology, Baltimore, Williams & Wilkins Company, 1940 (*b*) Walshe, F M R On the Pathogenesis of Diphtheritic Paralysis, Quart J Med **12** 14-37 (Oct) 1918-1919, (*c*) Forms of Peripheral Neuritis Among Troops Serving with the Egyptian Expeditionary Force, 1915-1919, Brain **43** 74-85 (May) 1920 (*d*) Norris, R F, Kern, R A, Schenck, H P, and Silcox, L E Diphtheria in Tropics Report of Eighteen Cases on a United States Naval Hospital Ship, U S Nav M Bull **42** 518-524 (March) 1944

2 Livingood, C S, Forrester, J S, and Perry, D Cutaneous Diphtheria Report of 140 Cases to be published

3 Kay, C F, and Livingood, C S Myocardial Complications of Cutaneous Diphtheria, Am Heart J, to be published

ulcers had developed In the remaining 31 cases, which comprised the B group, the patients either were referred from a forward hospital because their lesions were unusually slow to heal or sought admission because multiple neuritis developed after they had been discharged from their original hospital as recovered The number of cases of multiple neuritis which developed in the two groups is seen in table 1

The incidence of multiple neuritis as a complication cannot be accurately estimated from these figures, since many factors distort their validity, e g , the relatively small number of cases, factors of selection which determined the hospitalization of patients and, particularly, the fact that there is no accurate estimate of the total number of cases of cutaneous diphtheria The figures for the A group probably are more nearly representative of the incidence of the neuritic complication, although they, too, are probably weighted, since only the patients who were most severely ill were evacuated to a general hospital

All the patients with neuritis included in this study were treated as hospital patients When the neuritis began while the patient

TABLE 1.—*Incidence of Multiple Neuritis in Cases of Cutaneous Diphtheria*

	Number of Cases of Cutaneous Diphtheria	Incidence of Neuritis
Group A	109	37 (33 9%)
Group B	31	24 (77 4%)
Total	140	61 (43 5%)

was still in the hospital, he was transferred to the neurologic ward In those instances in which the neuritis became symptomatic after the patient's discharge he was admitted directly to the neurologic service The patient's progress was evaluated at weekly intervals by a complete neurologic examination Routine studies of the blood included determination of the sedimentation rate, a blood count and the Wassermann test Examinations of the spinal fluid were made at frequent intervals

All the patients were given the Schick test, but the data for this test are not included, since there was evidence to indicate that a portion of the test material was not satisfactory A number of the patients had been given diphtheria antitoxin before having the Schick test, a factor which further invalidated the statistics

The mode of transmission of the diphtheritic infection commonly is presumed to be human carriers Diphtheria is not rare among the natives, and this was the probable source of the infection A more detailed report of the epidemiology is being prepared by Livingood and associates [2]

Most of the cases of cutaneous diphtheria seen in this series developed in combat soldiers who were fighting under the adverse conditions of the monsoon The intense heat and the constant rain and humidity, together with the complete lack of facilities for any personal hygiene while in combat, caused the men to ignore the many minor injuries which they acquired This neglect resulted in secondary infection of these injuries In many instances this included infection with C diphtheriae with the development of the typical chronic ulcers of the skin of cutaneous diphtheria

At first there was a tendency on the part of medical officers to minimize the importance of such ulcers, treating the men on an active duty status This policy was dictated in part by military necessity, owing to the acute need for men, and in part by the failure of the physicians to diagnose these ulcers as cutaneous diphtheria Later, when the cause had been established and the clinical picture became more widely known, it was recognized that the ulcers of cutaneous diphtheria required early and adequate hospital care for prompt healing Actually, this policy reduced invalidism [2] Whether the duration of the cutaneous lesions has any bearing on the incidence of neuritis has not been established It is possible, however, that the chronicity of the lesions in many of these cases may have favored the development of this complication Neuritis was more likely to develop in those cases with the most severe and the greatest number of lesions However, there was no correlation between the severity of the cutaneous lesions and the severity of the neuritis The clinical aspects of the cutaneous diphtheria have been presented elsewhere [2]

Neuritis and, to a smaller degree, myocarditis are relatively common complications of untreated faucial diphtheria The incidence, however, of both neuritis and myocarditis can be reduced to a negligible factor by the prompt administration of antitoxin In this series myocarditis occurred in 5 per cent of the cases [3] There were 7 cases of myocarditis, 4 were verified and 3 were probable cases Of the 4 definite cases, neuritis was present in 3, and in the fourth death from cardiac failure occurred on the twenty-third day of the diphtheria In no case did neuritis develop earlier than the twenty-third day (see table 2) In only 1 of the 3 probable cases was neuritis present The myocarditis occurs much less frequently, appears earlier and is of shorter duration than the neuritis

Faucial diphtheria rarely occurred as a result of the cutaneous infection In 3 of the cases of neuritis faucial diphtheria later developed This had no obvious effect on the neuritis

CLINICAL PICTURE

The clinical picture of multiple neuritis associated with diphtheria displayed many variations although the basic pattern was constant

In many instances the neuritis developed while the ulcers were still active, in others the neuritis first became symptomatic several weeks after the ulcers had completely healed The average interval between the estimated date of onset [4] of the diphtheritic ulcers and the first evidence of neuritis was 70 4 days, the shortest interval was 23 days and the longest 158 days (table 2)

TABLE 2—*Interval, in Days, Between Onset of Ulcers and Onset of Neuritis*

	Interval		
	Average	Shortest	Longest
Group A	68 0	21	146
Group B	72 0	25	158
Both groups	70 4	23	158

While the date of onset of the diphtheritic infection is only estimated, it is interesting to note the correlation between the figures for the two groups shown in table 2

The neuritis began with involvement either of the cranial or of the peripheral nerves The frequency with which each was first implicated and the presenting symptom can be seen in table 3 In a few cases

TABLE 3—*Mode of Onset of the Neuritis*

Symptom	Number of Cases in Each Class *			Total Number
	Class 1	Class 2	Class 3	
A Cranial nerve involvement				
Loss of accommodation	1	8	8	17
Loss of taste and numbness of tongue		1		1
Weakness of palate and pharynx			2	2
B Peripheral nerve involvement (sensory)				
Numbness and tingling				
Hands	7	4		11
Feet	1	3		4
Both	10	12	3	25
C Peripheral nerve involvement (motor)				
Weakness of the extremities	1			1
Total	20	28	13	61

* The classes in table 3 were based on the severity of the neuritis In class 1 (cases of mild neuritis) there was only sensory involvement In class 2 (moderately severe) there were sensory signs and symptoms in addition to motor weakness and loss of tendon reflexes In class 3 (severe) there was definite muscular wasting in addition to the signs and symptoms listed under class 2 Involvement of the cranial nerves could occur in any class, in addition to the aforementioned symptoms

the onset was almost simultaneous, with involvement of both cranial and peripheral nerves As can be seen from table 3, the site of

4 Since most of the patients were not seen until some time after the ulcers had developed, the date of onset of the diphtheritic infection had to be estimated from the patient's description of the clinical development of the ulcer It is recognized that such an estimate cannot be exact, and probably is accurate only within plus or minus 15 days [2]

onset had considerable prognostic significance While cranial nerve palsies as the presenting symptom were almost equally common in classes 2 and 3, such a condition occurred only once in class 1 Consequently, the appearance of symptoms referable to the cranial nerves forecast moderately severe or severe neuritis In further support of this prognostic trend, severe neuritis developed in only 3 of the 40 cases in which onset was with phenomena referable to the peripheral nerves

The site of the cutaneous lesion or lesions appeared to play no role in determining where the neuritic symptoms would make their first appearance The distribution of the ulcers was generalized They occurred on the face, neck, chest, axilla, penis, buttocks and extremities, in many instances there were multiple lesions, widely scattered However, in 35 cases the lesions were limited to the lower extremities The neuritis in 4 cases of this group began with numbness and tingling of the feet alone, and in 6 others, with paresthesias of the hands In the remaining 25 cases the onset was either with paresthesias in all four extremities or with palsies of the cranial nerves In 25 of the remaining 26 cases of neuritis the cutaneous lesions were so scattered that no conclusions could be drawn concerning this point It is interesting to note that in the 1 final case, in which an extensive ulcer involved the entire anterior surface of the neck, there first developed numbness and tingling of the hands and feet, and not cranial nerve palsies, although later these did appear

The clinical course of the neuritis was slow and proceeded in regular sequence through certain definite steps While in some instances these steps were superimposed, in others they were quite discrete, being separated by a latent asymptomatic period The steps, in order of their appearance, were (*a*) cranial nerve, (*b*) peripheral nerve (sensory) and (*c*) peripheral nerve (motor) involvement Cranial nerve palsies developed in 21 (34 4 per cent) of the cases of neuritis In all these cases, in addition, the peripheral nerves were involved In 10 cases this involvement was largely confined to sensory changes while in 11 cases the motor components were also affected The multiple neuritis was limited to the peripheral nerves in the remaining 40 cases (65 6 per cent) In 19 of these cases the involvement was limited to the sensory nerves alone, i e, paresthesias and alterations in the various modalities of sensation were present (table 4) Motor neuritis occurred in 1 case In the other 20 cases mixed motor and sensory signs and symptoms were present The same sequence was maintained with regard to the clinical development of the neuritis even in the absence of cranial nerve palsies

The first symptom of dysfunction of the cranial nerves was usually blurred vision The patient noticed that he could not read unless the book was held farther away than was his custom On examination the patient would be found to have a change in his near point, although gross evidence of paralysis of accommodation was absent Other symptoms referable to the cranial nerves including difficulty in swallowing, hoarseness and diminished taste occurred less commonly The cranial nerve palsies lasted from ten to thirty days

TABLE 4.—*Frequency with Which Signs and Symptoms Occurred as Related to Severity of Neuritis*

Neurologic Symptoms and Signs	Total Incidence		
	Class 1	Class 2	Class 3
Cranial nerves			
(a) Loss of accommodation	2	8	10
(b) Numbness of tongue and loss of taste		2	3
(c) Weakness of Pharynx		1	4
Palate		2	5
Larynx			1
Peripheral nerves			
Upper extremity Sensory			
(a) Numbness and tingling	19	29	12
(b) Hypesthesia to pain and light touch	19	29	12
(c) Loss of vibration and position sensation			
Motor			
(a) Weakness of Shoulder		3	5
Arm		1	9
Hand	1	26	12
(b) Wasting			
Interosseus muscles		4	11
Generalized			6
(c) Loss of tendon reflexes	5	29	12
Lower extremity Sensory			
(a) Numbness and tingling	17	29	12
(b) Hypesthesia to pain and light touch	17	29	12
(c) Loss of vibration and position sensation	1	3	4
Motor			
(a) Weakness of Hip		2	6
Quadriceps	1	24	12
Feet		22	11
(b) Wasting			
		2	10
			6
(c) Re	6	29	12

As these symptoms were clearing up, or after an interval of a week to ten days, the first symptoms of involvement of the peripheral nerves would appear The patient then would notice numbness and tingling of the hands and feet At that time the patient generally showed no objective signs and if there had been no previous cranial nerve palsy the diagnosis could not be positively established However, in from one to two weeks these paresthesias would be followed by definite objective neurologic changes Examination then would disclose hypesthesia to pinprick and light touch in a glove and stocking distribution The sensory distribution varied from one involving only the distal segments (i e the fingers and toes) to one which

implicated nearly the entire extremity Diminished appreciation of heat and cold paralleled the hypesthesia to pain and light touch

Ataxia was a relatively rare symptom in the lower extremities and was never demonstrable in the upper extremities In 8 cases with ataxia there was definite impairment of vibration and position senses In 2 cases this appeared to be due to involvement of the posterior column, a sensory level for vibration being obtained at the eighth thoracic segment in 1 case and at the third lumbar segment in the other In the remaining cases the sensory changes were limited to the distal segments, being an additional sign of the multiple neuritis The sensory symptoms and signs persisted in general from four to eight weeks, although in a few cases they lasted up to ten weeks

In a number of cases the progress of the neuritis ended with the sensory symptoms but in 12 cases there was pronounced involvement of the motor components of the peripheral nerves While in an occasional case the motor symptoms developed simultaneously with the sensory, most commonly these did not appear until the end of the sensory period or after a latent period of one to four weeks The most common presenting symptom of motor involvement was the extreme fatigue which these patients noted after any exertion Neurologic examination at this point usually disclosed diminished strength or loss of tendon reflexes but no readily detectable gross motor weakness There were no pathologic reflexes, but the general muscular tone was diminished

Within a week to ten days definite muscular weakness would develop There was a tendency for certain muscles to be involved predominantly—i e, the interosseus muscles and the quadriceps In a few cases the motor weakness was extreme, involving all the extremities and the trunkal musculature In 2 instances the patients were completely bedridden, unable to do anything for themselves If the motor involvement was severe, muscular atrophy would appear, particularly in the muscle groups just enumerated The motor phase lasted from six to twelve weeks It was difficult at times to evaluate when there was complete return of function, since a few men continued to complain of easy fatigability after all objective signs had disappeared How often this was motivated by a disinclination to return to combat duty was questionable in a few cases All the men, however, recovered completely, and the majority were returned to full duty

Walshe,[5] in his analysis of cases of neuritis following cutaneous diphtheria, reported the frequent early involvement of nerves adjacent to ulcers, which he regarded as due to the local absorption of the

5 Walshe, loc cit

toxin Usually, in these cases the process would go on to development of signs and symptoms of multiple neuritis In only 1 of our cases was there a clinical course similar to this The patient had a solitary ulcer over the internal malleolus of the left ankle His first motor symptom was a left foot drop, although previously he had had involvement of cranial and peripheral (sensory) nerves The foot drop was quickly followed by symmetric motor involvement of all four extremities Although other patients had similar solitary ulcers, there were no other local nerve palsies

The scars of all the cutaneous ulcers, irrespective of whether neuritis had developed, showed varying sensory changes In the cases of deep penetrating ulcers the scars were anesthetic, and an area of hypesthesia of from 1 to 5 cm surrounded the scar The

TABLE 5.—*Duration, in Days, of Neuritis in All Cases Irrespective of Severity*

Group	Duration		
	Average	Shortest	Longest
A	109 5	23	184
B	92 3	21	163

TABLE 6.—*Average Duration, in Days, in Cases According to Severity of Neuritis*

Class	Group A		Group B		Combined	
	No of Cases	Duration	No of Cases	Duration	No of Cases	Duration
1 (mild)	12	77	8	65 7	20	71 3
2 (moderately severe)	18	117 1	11	95 09	29	106 1
3 (severe)	7	145 2	5	151 0	12	158 1

scars of the more superficial ulcers were hypesthetic In scars of the first type it seemed probable that the anesthesia was due at least in part to tissue destruction It should be noted, moreover, that any deep, penetrating scar, irrespective of its origin, may remain anesthetic for a long period, owing to tissue destruction The hypesthesia seen in the "normal" skin surrounding the deep ulcers and in the superficial scars was probably due to local absorption of toxin

There were no sphincter disturbances in any of our cases It was felt that this was significant, since a number of patients had ulcers on the buttocks and genitalia

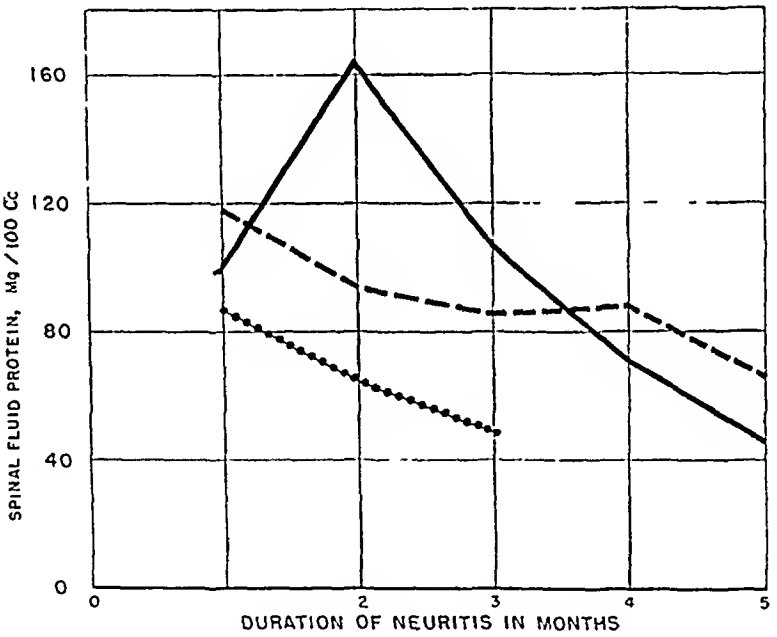
Muscular tenderness was never a prominent symptom, although it was not infrequently found Rarely was tenderness elicited by direct pressure on the nerve trunks

The duration of this neuritis was prolonged by the slow sequence of its development (tables 5 and 6) In the average case of neuritis the duration was about one hundred days

The duration was directly dependent on the severity of the neuritis For class 1 the average length was seventy-one days, for class 2, one hundred and six days, and for class 3, one hundred and thirty-eight days There were no residuals, all of the patients recovered completely

LABORATORY STUDIES

All these patients had complete laboratory studies, Blood counts, urinalyses and Wassermann tests of the blood disclosed nothing significant The blood sedimentation rates were all within normal limits Examination of the spinal fluid showed a pronounced albumin-ocytologic dissociation The cell count was never increased, but the protein was found to be increased early, and this increase persisted throughout the neuritis, gradually returning to within normal



In this graph, the average value of the protein of the spinal fluid for each class is shown The values for class 1 are shown by the line of dots, the values for class 2, by the broken line, and the values for class 3, by the solid line

limits The rise in protein was usually proportional to the severity of the disease, in 1 case it reached 317 mg per hundred cubic centimeters (graph) This alteration in the protein content of the spinal fluid was helpful in estimating the disability of a number of the men who continued to complain of weakness after all objective evidence of the neuritis had disappeared In many of these men it was found that the protein level remained high Later, when it had fallen within normal limits, the patients were asymptomatic

Material was obtained from all the lesions and cultured for C diphtheriae, and tests for virulence were performed on the positive cultures [3] The results of these laboratory studies are outlined in table 7 While

the total number of patients with cultures of C diphtheriae which proved virulent was only 25 (17.8 per cent), this does not give a complete picture. During the first six weeks during which the majority of these patients were admitted to the hospital none of the cultures were positive for virulent C diphtheriae, although the diagnosis of cutaneous diphtheria was strongly suspected on clinical grounds. This failure to obtain a higher percentage of positive cultures of the virulent organisms was attributable partly to inadequate culture mediums. When this situation was remedied by material flown from the United States, the number of patients whose condition

TABLE 7.—*Results of Examinations of Cultures of Material from Ulcers*

	Group A	Group B	Total
Number of cases in which virulent C diphtheriae organisms were isolated	23 (21%)	2 (6.2%)	25 (17.8%)
Number of cases in which organisms with morphologic character of C diphtheriae were isolated	51 (46.8%)	12 (37.5%)	63 (45.0%)
Number of cases in which other organisms (hemolytic Staphylococcus aureus, hemolytic and nonhemolytic streptococci) were isolated	35 (32.2%)	*	

* Many of the patients in group B came in because of their neuritis after the lesions were largely healed.

was diagnosed clinically as cutaneous diphtheria and who were proved to have infections with virulent C diphtheriae rose to approximately 80 per cent. Cultures of material from the nose and throat were made for all these patients routinely. Only 1 patient with virulent C diphtheriae in the nasopharynx was found. From 13 other patients organisms with the morphologic characteristics of C diphtheriae were isolated. It is quite probable that these results might have been different had adequate culture studies been possible from the beginning.

TREATMENT

Treatment of the cutaneous lesions and the myocarditis has been discussed elsewhere.[6] The treatment of the neuritis is largely preventive by the early administration of diphtheria antitoxin in adequate dosage. Unfortunately, many of the patients did not receive antitoxin, or it was not administered early in the course of their cutaneous diphtheria. The only patients who afforded any information as to the effectiveness of antitoxin in the prevention of complications was the A group, who were studied throughout their illness at one hospital. However, this group is not statistically significant, since the number of cases is so limited. The incidence of neuritis was greatly reduced by the administration of antitoxin (table 8).

6. Livingood and others.[2] Kay and Livingood.[3]

Neuritis occurred in only 14 per cent of the patients if antitoxin was given before the thirty-second day and in 30 per cent if it was given later than this On the other hand, the rate rose steeply to 61 per cent if no antitoxin was given As in cases of faucial diphtheria, it would appear that antitoxin is of primary importance in the prevention of neuritis

An interesting observation was made on the duration of the neuritis in the patients who received antitoxin Twenty-five of the 61 patients with neuritis were given antitoxin, although for 18 of these

TABLE 8—*Influence of Antitoxin* on Incidence of Neuritis in Patients with Cutaneous Diphtheria*

	Group Given Antitoxin		
	Before 32d Day †	After 32d Day †	Untreated Patients
Number of patients	42	36	31
Number with neuritis	6 (14 2%)	10 (30 6%)	19 (61 2%)

* The dose of diphtheria antitoxin varied from 20,000 to 40,000 U S P units
† Number of days after onset of the cutaneous diphtheria that antitoxin was given

25 men this was after the thirty-second day of the infection As can be seen in table 9, antitoxin was administered to 21 of 37 patients of the A group and to only 4 of the 24 patients of the B group In the light of this observation it is interesting to compare the duration of the neuritis in the two groups (tables 5 and 6) Actually, the A group, in all classes, had a longer period of disability due to their neuritis than the B group

TABLE 9—*Number of Patients with Neuritis Who Received Diphtheria Antitoxin*

	Group A	Group B
Before 32d day *	6	1
After 32d day *	15	3
Total	21	4

* Number of days after onset of the cutaneous diphtheria that antitoxin was given

Once the neuritis developed, no therapeutic measures appeared to influence the course of the illness One-half the patients were placed under treatment with multivitamins and vitamin B complex, but this did not shorten the period of disability For those patients in whom marked muscular wasting developed physical therapy was of value Unfortunately, the demands on the physical therapy department were so great that only a few of the most severely affected patients could be given this form of treatment consistently All the patients were encouraged to take part in the reconditioning program as rapidly as their recovery would permit Graduated exercises

were given, and each patient was told to stop as soon as fatigue was noticed The amount of exercise was increased as quickly as the clinical progress would allow

REPORT OF CASES

The 3 cases outlined here were chosen because they illustrate the typical clinical picture of this form of multiple neuritis

CASE 1 (class 1) —The soldier had a number of abrasions and insect bites which developed into typical diphtheritic ulcers, these lesions were undiagnosed for several weeks On admission he had multiple, small diphtheritic ulcers on his feet and legs Culture of material from the ulcers yielded virulent C diphtheriae organisms There was no evidence of neuritis at this time Shortly after admission to the hospital, on the thirty-third day of his illness, he was given 20,000 U S P units of diphtheria antitoxin The ulcers healed completely in the next four weeks On the sixty-second day the first symptoms of neuritis were noted, i e, numbness and tingling of the fingers and hands Neurologic examination at this time revealed no objective signs About a week later the paresthesias had extended to the feet and legs and had involved the forearms Examination at this time disclosed definite hypesthesia to pinprick and light touch The picture then remained unchanged for two weeks, but in the next four weeks there was a gradual return of sensory function The tendon reflexes were diminished, but there was no other subjective or objective evidence of motor involvement The reflexes did not return to normal until the eighty-seventh day Determination of the protein content of the spinal fluid in this case gave the following values

Day of Neuritis	Protein, Mg /100 Cc
5	120
21	137
61	87
87	42

CASE 2 (class 2) —The patient had a number of ulcers on his hands, arms and back, many of them due to shrapnel wounds Prior to admission to the Twentieth General Hospital he had been treated in a forward medical unit On his admission to the general hospital physical examination revealed only a number of ulcers characteristic clinically of cutaneous diphtheria Culture of the ulcers yielded virulent C diphtheriae On the forty-fourth day of his illness he was given 40,000 U S P units of diphtheria antitoxin The ulcers were slow to heal, finally clearing on the one hundred and first day

On the seventieth day of his illness the patient noticed blurred vision and diminished taste sense Neurologic examination then showed only alteration in the visual near point and impairment of taste sense The cranial nerve palsies had disappeared in two weeks One week later he noted numbness and tingling of his hands and feet, which later involved the forearms and legs Examination then disclosed anesthesia to pinprick and light touch over the hands, forearms, feet and legs up to the knees There was diminished appreciation of heat and cold in the same distribution These sensory symptoms cleared in the next four weeks Toward the end of this period the deep reflexes became hypoactive, and the patient noted generalized weakness, which was most pronounced in his legs when he tried to walk up or down stairs and less in the hands All the deep reflexes were absent, and there was definite weakness of the extremities, the quadriceps and the interosseus muscles being most severely affected, there

was no wasting During the next eight weeks there was slow but complete motor recovery Determination of the protein of the spinal fluid gave the following values

Day of Neuritis	Protein, Mg /100 Cc
2	127
13	223
21	210
32	175
67	87
90	70
120	53

CASE 3 (class 3) —The soldier had multiple ulcers on his hands and feet He was admitted relatively early in the course of his diphtheritic infection and was given 20,000 U S P units of diphtheria antitoxin on the twenty-second day His ulcers responded rapidly and were completely healed by the sixty-ninth day At about the end of the fifth week after the onset of the ulcers he noticed blurred vision and difficulty in swallowing Neurologic examination revealed only alteration in the near point and paresis of the palate A few days later he noticed diminished taste sensation These symptoms had entirely disappeared by the twenty-second day Three days later he reported numbness and tingling of the distal segments of all four extremities He reported that he could not walk in the dark Neurologic examination disclosed anesthesia to pinprick, temperature and light touch, involving the distal two thirds of all four extremities In addition, vibration sense was absent at the ankles but was retained elsewhere, and position sense was lost in the big toes The sensory changes gradually disappeared after six weeks, but during the last week he became aware of weakness and easy fatigability This was quickly followed by areflexia, pronounced objective weakness of all extremities and, finally, generalized wasting Return of motor power was extremely slow, but he had completely recovered by the one hundred and sixtieth day Values for the protein content of the spinal fluid were as follows.

Day of Neuritis	Protein, Mg /100 Cc
10	160
41	244
60	260
80	234
130	143
147	115
158	60

SUMMARY

Clinical and laboratory observations in 61 cases of multiple neuritis which developed as a complication in 140 cases of cutaneous diphtheria are reported Characteristic of this syndrome is the late onset of the neuritis after the development of the diphtheritic ulcers The neuritis began either with symptoms referable to the cranial nerves or paresthesias involving the peripheral nerves During the clinical development of the neuritis it passed through one or more of the various stages, i e, cranial nerve, peripheral sensory nerve and peripheral motor nerve involvement Neither the cranial nerve nor the peripheral motor nerve stage appeared in all cases, but all stages usually occurred in cases of severe neuritis In 2 cases evidence of a pathologic process in the posterior column was disclosed

This type of multiple neuritis is distinguished by its slow and insidious course from the more rapidly developing syndrome seen in the infectious polyneuritis of Guillain and Barre While the albuminocytologic dissociation of diphtheritic multiple neuritis resembles that found in the Guillain-Barre syndrome here too there is dissimilarity, since the elevation of the protein in cases of the latter syndrome is much higher

The laboratory examinations show no consistent changes except for the albuminocytologic dissociation found in the spinal fluid in nearly every case The elevation of spinal fluid protein is usually proportional to the severity of the neuritis

Recovery is slow particularly in cases in which there is motor involvement, but in every case in this series it was complete

There is little evidence to suggest that local absorption of the toxin played any role in the development of the neuritis

CONCLUSIONS

1 Multiple neuritis is a frequent complication of cutaneous diphtheria The early administration of diphtheria antitoxin in adequate dosage significantly reduces the incidence of this complication

2 The clinical development of diphtheritic multiple neuritis is slow and proceeds through a variable number of definite steps

3 This march of events does not indicate that there is a relationship between the site of the cutaneous lesions and the development of the symptoms

4 Local paralyses occur rarely and do not appear to play a major role in the development of the clinical picture

5 A Guillain-Barre type of albuminocytologic dissociation is a concomitant of this form of multiple neuritis and is of considerable value in following the course of the disease

6 There is no specific treatment for this type of multiple neuritis

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PROGNOSIS IN SO-CALLED SCIATIC NEURITIS

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IN RECENT years a common neurologic disease called sciatic neuritis has been found to be caused, in the majority of cases, by herniation of the nucleus pulposus in a lower lumbar intervertebral disk with pressure on nerve roots of the cauda equina Aware of the belief of some authors that primary sciatic neuritis is a distinct clinical entity (Alpers, Gaskill and Weiss [1]), I maintain that the symptoms and signs of herniation of the nucleus pulposus in the fourth or fifth lumbar intervertebral disk are indistinguishable from the well defined syndrome that was formerly called sciatic neuritis Cessation of pain after removal of herniated nuclei has been so impressive that whenever this characteristic syndrome appears the question of spinal operation demands consideration However, cessation of pain has been observed without spinal operation with sufficient frequency to justify the assumption that the defect may be repaired by natural processes Indeed there is such evidence in the literature In 1939 Ekvall [2] reported on the condition of 74 hospitalized patients four to five years after the diagnosis of sciatica had been made Twenty were free from sciatica In the remaining 54 patients there was persistence of symptoms, but in 27 of these patients capacity for work was good, even for hard manual labor in 21 In 1944 Grant [3] reported follow-up observations on 93 patients whose sciatica was believed to be due to herniated intervertebral disk but who were not subjected to spinal operation There was complete recovery in 9 out of 15 bedridden patients and in 12 out of 42 patients unable to work

In the records of the New York Hospital the diagnosis of sciatic neuritis has been virtually supplanted by that of herniation of the fourth or fifth lumbar intervertebral disk Assuming that in the majority of cases in which the diagnosis was sciatic neuritis the condition was

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1 Alpers, B J , Gaskill, H S , and Weiss, B P The Problem of Primary Sciatic Neuritis An Analysis of Fifty-Five Cases, Am J M Sc **205** 625 (May) 1943

2 Ekvall, S Enquête clinique, au printemps de 1938, sur les cas de sciatique observes durant les annees 1933 et 1934, Acta med Scandinav **101** 1, 1939

3 Grant, F G Operative Results in Intervertebral Discs, J Neurosurg **1** 332 (Sept) 1944

herniated disk, follow-up information would determine the natural history of this condition and thereby establish a basis for comparing surgical and conservative methods of treatment Accordingly, by means of questionnaires and reexaminations, satisfactory follow-up information was obtained in 55 cases in which the condition was reliably diagnosed as sciatic neuritis and in which, after careful consideration of the symptoms and signs, there seemed to be no reasonable doubt that the trouble would now be classified as herniation of the fourth or fifth lumbar intervertebral disk Most of the patients were private and ward patients in the New York Hospital, 2 were outpatients, 1 was admitted to the neurologic service of Bellevue Hospital, and 4 were physicians on the staff of the New York Hospital All were severely afflicted and had pain in the posterior or posterolateral aspect of one leg, which was increased by stretching the sciatic nerve of the affected leg Additional symptoms and signs were pain in the lumbosacral region, tenderness in the region of pain, increase of pain on raising the intra-abdominal pressure, as by straining during defecation, diminution or absence of the ankle jerk and, in the distribution of nerve roots from the fourth lumbar to the second sacral segment inclusive, weakness of muscles, paresthesia and decreased cutaneous sensation The methods of treatment were numerous, but no patient had a spinal operation The follow-up period began with the first attack in which a reliable diagnosis of sciatic neuritis was made and ranged from one year and three months to twenty-three years, with an average of five years and one month

The patients were grouped as follows

1 Patients who have been continuously free from pain in the leg and lower part of the back since the subsidence of the first attack For these recovered patients the duration of pain in the leg ranged from eleven days to three years, with an average of seven months The period since recovery ranged from one year to seven years and eight months, with an average of three years and five months

2 Patients who have had persistence, recurrence or development of pain in the lower part of the back since the subsidence of pain in the leg Inconsequential and considerable degrees of pain were reported, but none of the patients mentioned disability from it

3 Patients who have had persistence or recurrence of pain in the leg with or without pain in the lower part of the back Three degrees of pain could be defined inconsequential and not interfering with former activity, considerable but permitting relatively light work, disabling or not permitting any material physical work In the last category was placed a man who had never done much physical work but who had become addicted to the use of cathartics because straining during defeca-

tion was so painful Also placed in this category were the 5 patients who eventually had a spinal operation, with resulting relief from pain in each instance Three of these operations were referred to as "spinal fusion", 1 was called a "spinal operation", the other is known to have been the removal of a herniated nucleus pulposus in the fourth lumbar intervertebral disk The follow-up results are shown in table 1

TABLE 1.—*Results for 55 Patients with So-Called Sciatic Neuritis Who Were Followed from One and a Quarter to Twenty-Three Years*

	Satisfactory		Unsatisfactory	
	Number of Patients	Per Cent	Number of Patients	Per Cent
Free from pain	20	36		
Pain in lower part of back only				
Inconsequential	2	4		
Considerable			2	4
Pain in leg				
Inconsequential	8	14		
Considerable			16	29
Disabling			7	13
Total	30	54	25	46

The follow-up information offered an opportunity to determine whether the prognosis in cases of so-called sciatic neuritis could be predicted by clinical or laboratory observations Accordingly, the data on the neurologic signs, namely, the motility and sensory dysfunctions indicating nerve injury, and the total protein content of the spinal fluid, which was the only abnormality revealed by lumbar puncture in these patients, have been tabulated to show any differences in incidence between the patients who had a satisfactory result and those who had an unsatisfactory result As shown in table 2, there was no difference in the incidence of impairment of the ankle jerk, whereas decreased sensation and weakness were more frequent in the group with a satisfactory

TABLE 2.—*Incidence of Neurologic Signs as Related to Result*

	Group with Satisfactory Results, per Cent	Group with Unsatisfactory Results, per Cent
Impaired ankle jerk	50	48
Decreased sensation	40	24
Weakness	17	8

outcome As shown in table 3, there was no essential difference in the total protein content of the spinal fluid in the two groups With 45 mg per hundred cubic centimeters as the upper limit of normalcy, the protein

content was above this level in approximately half the cases of both groups

The sex and age distributions in the two groups were as follows In each group there were almost twice as many males as females In the group with a satisfactory result the ages of the patients at the time

TABLE 3.—*Protein Content of Spinal Fluid as Related to Outcome in Cases of So-Called Sciatic Neuritis*

Satisfactory Result (14 Cases)	Unsatisfactory Result (12 Cases)
30 mg per 100 cc	10 mg per 100 cc
30 mg per 100 cc	27 mg per 100 cc
30 mg per 100 cc	30 mg per 100 cc
30 mg per 100 cc	30 mg per 100 cc
40 mg per 100 cc	35 mg per 100 cc
40 mg per 100 cc	40 mg per 100 cc
50 mg per 100 cc	40 mg per 100 cc
50 mg per 100 cc	50 mg per 100 cc
50 mg per 100 cc	50 mg per 100 cc
75 mg per 100 cc	75 mg per 100 cc
75 mg per 100 cc	100 mg per 100 cc
100 mg per 100 cc	50 100, 200 mg per 100 cc
100 mg per 100 cc	(3 taps)
75 100 mg per 100 cc (2 taps)	

of the first reliably diagnosed attack of sciatica ranged from 26 to 58 years, with an average of 45 years, in the group with an unsatisfactory outcome the ages ranged from 24 to 63 years, with an average of 38 years This difference in age distribution suggests that the prognosis is better in the older age period

For the purpose of therapeutic evaluation Dr Bronson S Ray [4] has submitted follow-up information on 82 of 100 patients from the New York Hospital on whom he operated for the removal of a

TABLE 4.—*Comparison of Results of Conservative and Surgical Treatment*

	Patients Without Operation (55), per Cent	Patients With Operation (82) (Ray), per Cent
Recovery	36	60
Residual symptoms		
Inconsequential	18	26
Considerable	33	12
Disabling	13	2

herniated nucleus pulposus in the fourth or fifth lumbar intervertebral disk The symptoms and signs in these patients undoubtedly would have led, in earlier times, to the diagnosis of sciatic neuritis The operative procedures and observations were as follows removal of a

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herniated nucleus pulposus, 76 cases, removal of an unherniated degenerated nucleus pulposus from a ruptured disk, 13 cases, decompression of nerve roots without removal of the nucleus pulposus from an incompletely ruptured disk, 3 cases, no detectable disease of the disk, 8 cases In table 4 the follow-up results for six months or longer are compared with those for the patients on whom operation was not performed

CONCLUSIONS

1 In a series of cases of the syndrome formerly called sciatic neuritis and now known to be caused, in the majority of instances, by herniation of the nucleus pulposus in the fourth or fifth lumbar intervertebral disk the prognosis was satisfactory without spinal operation in 54 per cent

2 Although in this series removal of the herniated nucleus promptly relieved pain and bettered the prognosis by 32 per cent, natural processes should be given an opportunity to repair the defect before spinal operation is urged

3 Neurologic signs and the protein content of the spinal fluid are of no prognostic value

SIMILARITY OF CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCES ON RIGHT AND LEFT SIDES IN RESTING MAN

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THE cerebral arteriovenous oxygen differences have frequently been determined in man without taking into consideration whether the venous blood was drawn from the right or the left internal jugular vein Nevertheless, textbooks of anatomy state that the two internal jugular veins do not necessarily drain symmetric portions of the brain This difference in drainage has been emphasized by Gibbs and Gibbs [1] and, more recently, by Batson [2] Only rarely is there a torcular Herophili, a single chamber, in which the venous blood from the cerebral hemispheres and from the basal ganglia mix Usually the superior longitudinal sinus directs most of its blood to one or the other of the lateral sinuses, while the straight sinus sends its blood to the opposite side Riggs, cited by Kety and Schmidt [3] examined 25 autopsy specimens and observed that most of the blood from the superior longitudinal sinus went to the right side in 15 specimens In 9 specimens the blood from the superior longitudinal sinus in its entirety went to the right lateral sinus and in 1 specimen, to the left lateral sinus Knowledge of the venous drainage and of the fact that the higher cerebral parts [4] possess a faster rate of metabolism than the lower

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This investigation was aided by a grant from the Winthrop Chemical Company Research Fund

Mrs Ilse Memelsdorff made the determinations of the glucose and lactate contents of the blood

1 Gibbs, E L, and Gibbs, F A The Cross Section Areas of the Vessels That Form the Torcular and the Manner in Which Flow Is Distributed to the Right and to the Left Lateral Sinus, Anat Rec **59** 419-426, 1934

2 Batson, O V Anatomical Problems Concerned in the Study of Cerebral Blood Flow, Federation Proc **3** 139-144, 1944

3 Kety, S S, and Schmidt, C F The Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations, Am J Physiol **143** 53-66, 1945

4 Himwich, H E, and Fazekas, J F Comparative Studies of the Metabolism of the Brain of Infant and Adult Dogs, Am J Physiol **132** 454-459, 1941

(Footnote continued on next page)

areas of the brain might lead one to conclude that the arteriovenous oxygen differences on the right and the left sides, in a resting subject, would not be the same, owing to an unequal uptake of oxygen Most previous work on metabolism of the brain seems to have been done without consideration of the sources of the cerebral blood, on the assumption that the arteriovenous oxygen differences are the same on the two sides It is, therefore, the purpose of the present investigation to compare the arteriovenous differences when the venous blood is collected from the right and from the left internal jugular vein

METHOD

The subjects, examined in the postabsorptive state, were patients with mental disease, most of whom had a disorder diagnosed as schizophrenia Samples of blood were collected with the use of procaine anesthesia while the subjects were lying quietly in bed Either the right or the left internal jugular vein was tapped first, the order alternating in successive patients [5] Immediately thereafter, the opposite internal jugular vein was tapped, and finally blood was drawn from the brachial artery The blood was kept in glass containers over mercury, as previously described,[6] and was analyzed for oxygen,[7] glucose [8] and lactic acid [9] Oxygen analyses checked to 0 2 volume per cent, and it was found that variations of 1 volume per cent between the arteriovenous oxygen differences on the right and on the left side were within the experimental error In order to assure accuracy, the samples of blood used for the analyses of glucose and lactic acid were measured from a 1 cc Van Slyke pipet Differences in amounts of glucose and lactic acid of 4 and 1 2 mg, respectively, were considered significant In preliminary observations, it was noted that when the subject exhibited unrest, tension, excitement or active resistance the variations between the arteriovenous oxygen differences on the two sides were significantly greater than the normal average otherwise obtained in a quietly resting subject and were often beyond the experimental error of 1 volume per cent To maintain a comparison of arteriovenous oxygen differences in resting man, an attempt was made to overcome this difficulty by selecting subjects who it was felt would cooperate, and if that cooperation did not exist the collection of the samples of blood was discontinued

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Himwich, H E , Sykowski, P , and Fazekas, J F A Comparative Study of Excised Cerebral Tissues of Adult and Infant Rats, ibid **132** 293-296, 1941

5 Myerson, A , Halloran, R D , and Hirsch, H L Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch Neurol & Psychiat **17** 807-808 (June) 1927

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9 Barker, S B , and Summerson W H The Colorimetric Determination of Lactic Acid in Biological Material, J Biol Chem **138**.535-554, 1941

RESULTS

In 40 observations on the oxygen contents of both internal jugular veins and the brachial artery there was a variation in arteriovenous differences of from 0.00 to 1.00 volume per cent, inclusive, between the two sides in 33 patients and from 1.01 to 1.57 volumes per cent in 7 patients. The average variation for all observations was 0.59 volume per cent. There was no specific pattern, for in the group of 33 patients the differences on the right side were greater than on the left side in 14 patients and greater on the left side than on the right side in 18 patients, and in 1 patient the differences for the two sides were equal. Of the other 7 patients, the differences on the right side were greater than those on the left side in 4 and greater on the left side than on the right side in 3.

In 26 observations on the arteriovenous glucose differences, the brain absorbed glucose in 25 patients, and the result was within the experimental error in 1 patient. In 25 observations on the arteriovenous lactate differences, that substance was poured out of the brain in 13 patients and was taken up only once, and the results were within the experimental error for 11 patients. It is striking that in 12 of 15 pairs of values for arteriovenous glucose differences on the two sides and in 9 of 14 pairs of values for arteriovenous lactate differences the components of each pair agreed within the experimental error of the method.

COMMENT

Agreement Between Arteriovenous Oxygen Differences on the Two Sides.—In 33, or 82.5 per cent of these observations, the arteriovenous oxygen differences on the two sides agreed to within 1 volume per cent or less, and in 7, or 17.5 per cent the differences were in accord from 1.01 to 1.57 volumes per cent. Since the samples of blood were not drawn simultaneously, but in rapid succession, it is possible that differences beyond 1 volume per cent represent changes in the patient's condition, which may have been caused by the transient, painful stimulus which necessarily disturbed the desired resulting state. Whatever the cause for the deviations in some patients, it is important to note the significant agreement between the arteriovenous oxygen differences for the right and for the left side in most subjects. This agreement is not limited to the data for oxygen for usually both members of each pair of arteriovenous glucose differences and each pair of arteriovenous lactate differences were also in agreement with each other. The fact that glucose is absorbed by the brain and lactic acid is poured out by that organ[10] confirms previous work. More important

10. Nims, L. F., Gibbs, E. L., and Lennox, W. G.: Arterial and Cerebral Venous Blood Changes Produced by Altering Arterial Carbon Dioxide, J. Biol. Chem. **145**: 189-195, 1942.

in view of the agreement between the arteriovenous oxygen differences for the two sides is the observation that in most instances the arteriovenous glucose differences and the arteriovenous lactate differences were also in agreement, a phenomenon which extended to include the arteriovenous pyruvate differences[11] for the two sides

Physiologic Basis—Not all areas of the brain metabolize at the same rate In general the newer phyletic layers possess a faster metabolism[4] It is surprising that the internal jugular vein draining the major portions of the cerebral hemispheres does not exhibit a greater arteriovenous oxygen difference than the opposite vein The question arises whether the vascularity of any given cerebral region is related to the rate at which its oxidations take place

An investigation of this problem was undertaken by Craigie,[12] who studied the relative vascularity in the component parts of the rat brain He found that the gray matter is more vascular than the white and that gray matter may be sharply divided into two groups, the motor nuclei and the nuclei with higher integrative functions, the latter being most richly supplied with blood vessels He concluded that the differences in vascularity implied a corresponding degree of metabolic activity in the regions concerned

Dunning and Wolff[13] made similar studies on the cat They found that the white matter in the brain has the lowest vascularity, and since it possesses the lowest metabolic rate[14] this correlation is in agreement with Craigie's hypothesis Not only does the gray matter differ from the white, but in the cat, as in the rat, the various parts of the gray matter differ among themselves as to vascularity According to Dunning and Wolff,[13] the differences probably resemble the order of the metabolic rates in the same cerebral areas

The observation that the right and the left internal jugular vein usually contain similar volumes of oxygen in the quietly resting subject can, therefore, be explained if the parts of the brain with intrinsically lower metabolic rates possess a smaller structural vascular accompaniment With such an arrangement, the region receiving the smaller amounts of blood would also consume less oxygen, tending toward an

11 Himwich, W A, and Himwich, H E Pyruvic Acid Exchange of the Brain, J Neurophysiol **9** 133-136, 1946

12 Craigie, E H On the Relative Vascularity of Various Parts of the Central Nervous System of the Albino Rat, J Comp Neurol **31** 429-464, 1919-1920

13 Dunning, H S, and Wolff, H G The Relative Vascularity of Various Parts of the Central and Peripheral Nervous System of the Cat and Its Relation to Function, J Comp Neurol **67** 433-450, 1937

14 Holmes, E G Oxidations in Central and Peripheral Nervous Tissue, Biochem J **24** 914-925, 1930

equalization of the oxygen content in the right and the left cerebral venous return This hypothesis can be tested by determining simultaneously the arteriovenous oxygen difference and the blood flow on the right and those on the left side

SUMMARY AND CONCLUSIONS

In 40 observations on resting human subjects with mental diseases, the cerebral arteriovenous oxygen differences for the two internal jugular veins varied from 0 00 to 1 00 volume per cent in 33 subjects and from 1 01 to 1 57 volumes per cent in 7 subjects Similarly, in 12 of 15 determinations of arteriovenous glucose differences for the right and the left jugular vein and in 9 of 14 determinations of arteriovenous lactate differences for the right and the left jugular vein the members of each pair differed from each other only within the experimental error This agreement is surprising in view of the fact that the two internal jugular veins do not necessarily drain symmetric portions of the brain In explanation of this agreement, it is suggested that the vascular structure of any given cerebral region is in proportion of its metabolic demands

NOTE.—The paper by Gibbs Lennox and Gibbs (Bilateral Internal Jugular Blood Comparison of A-V Differences Oxygen-Dextrose Ratios and Respiratory Quotients, *Am J Psychiat* 102 184-190 1945), which has appeared since our own communication was submitted for publication, likewise points out the similarity of the cerebral arteriovenous differences on the right and left sides

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PHENOMENA OF SENSORY SUPPRESSION

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RECENTLY Bender and Furlow [1] reviewed the literature and described their case of an interesting sequel to cerebral injury similar to a syndrome first noted during World War 1 Briefly, this syndrome consists in the extinction, suppression or obscuration of the perception of an object in an "affected" field of vision when an object is presented simultaneously on the other, or "normal," side of the central point of fixation In persons with this disturbance, who have suffered injuries primarily of the parieto-occipital cortex, an object is visible in the "affected" field provided there is no strong stimulation in the unaffected field This phenomenon had previously been attributed by various authors to a defect in the patient's attentiveness Bender and Furlow, however, pointed out in their report that the factor of attention provides only a partial explanation of what occurs in the syndrome They elucidated the matter further by using Goldstein's proposal [2] that the phenomenon may be due to the lability of threshold in the damaged cortex, which needs more energy than the normal Moreover, one must consider rivalry and dominance mechanisms of the two cerebral hemispheres in explanation of the psychologic mechanisms underlying the phenomenon

In a later paper Bender [3] noted similar competitive mechanisms between cutaneous sensations on the two sides of the body in patients with lesions of the parietal cortex

The syndrome has many variations and degrees of intensity In some patients it is the basis of their major complaint, in others it is accidentally discovered Five cases of the condition were observed in an Army general hospital, and a new clinical feature in 2 of these cases leads to the following report, which substantiates in the main the previous observations and provides additional information in understanding the complicated mechanisms involved

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Read at a meeting of the New York Neurological Society, Dec 11, 1945

1 Bender, M B, and Furlow, L T Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch Neurol & Psychiat **53** 29-33 (Jan) 1945

2 Goldstein, K, in discussion on Bender and Furlow [1]

3 Bender, M B Extinction and Precipitation of Cutaneous Sensations, Arch Neurol & Psychiat **54** 1-9 (July) 1945

REPORT OF CASES

CASE 1.—A 24 year old soldier was struck on the head by a falling log. A nail protruding from the log penetrated his skull in the left occipitoparietal area 2 cm. from the midline. He was unconscious only momentarily but was dazed for a few minutes. Immediately on regaining consciousness, he noted that voices sounded as though they were in the distance, in addition, he had a great deal of difficulty with his vision. He was hospitalized within twenty minutes. He found that he was most comfortable while keeping the eyes closed. That night he had fever and vomited. The next day he was operated on, the details of the operation are not known except that he was told that "a little blood was washed out." Ten days after the operation he had fever again and an extremely severe headache, lasting three or four days. He received penicillin for four days, and the fever subsided. The headaches persisted for two weeks, and he was then evacuated from the combat zone. Gradually his vision began to improve, but for two months he could not see to the right. After a period of convalescence he was returned to duty.

Eight months after the accident, while talking to friends, he suddenly saw straight "bars" before his eyes and fell unconscious. His friends told him that he had a generalized convulsion. He was confused and groggy. He spent the next four days in bed. During this time his vision was blurred again but gradually returned to normal. Six weeks later, while seeing a movie, he suddenly saw spots before his eyes and lost consciousness for fifteen minutes, during which he had a convulsion. This second convulsion led to his being sent to the hospital for study, ten months after his injury.

He gave the following information concerning visual disturbances which he had noticed ever since recovery from the acute phase of his illness. While playing Ping-pong, he would frequently miss the ball if it was to his right. While driving a car, he was not certain whether he had passed an object to his right or not. His reading ability had slowed up considerably. He frequently made mistakes in writing and was not aware of the error in spelling until he was writing the next word. He had often noticed some difficulty in finding the right word in speaking and frequently had to ask people to repeat what they had said to him. At movies or at shows he noted that he could not recognize jokes or funny actions as quickly as he used to. Nevertheless, he did not think his sense of humor was impaired. He had not noted any emotional disturbances or change in appreciation of music, but when he tried to read music he had great difficulty in interpreting what he saw. He had never noted any difficulty in the appreciation of color.

At drill he noted that he frequently bumped into the soldier on his right. He was disturbed to find himself confusing right and left. By the time he was admitted for study, however, all the aphasic manifestations had disappeared.

He noted also that when he was perfectly still he could judge distances very accurately. However, if he was moving or driving a car, he had difficulty in judging distance. For instance, when playing basketball, he could shoot accurately while standing perfectly still, but if he tried to shoot while moving he made frequent errors. This observation is reminiscent of some of the disturbances noted by Riddoch.[4]

4. Riddoch, G.: Visual Disorientations in Homonymous Half-Fields, Brain 58: 376-382, 1945.

After he had returned to duty, his visual difficulties led him to report on sick call several times Each time visual acuity and perimetric measurements were normal He was told there was nothing wrong with his eyes and that he was probably "imagining" his complaints

Physical examination eleven months after his injury revealed no abnormalities He was right handed and right eyed His intelligence was superior Neurologic examination revealed that motor power was excellent throughout, all deep and superficial reflexes were active and equal on the two sides, with no pathologic reflexes Sensation, coordination and the cranial nerves were entirely normal Visual acuity was 20/20 in each eye Form and color fields were entirely normal Roentgenograms of the skull revealed no abnormalities Electroencephalographic study (Major Robert L Craig) showed a normal, 10 per second rhythm in all leads, but with asymmetry in amplitude, the waves from the right occipital lead being of higher amplitude than those from the left An occasional isolated spike occurred in the left frontal lead Hyperventilation was not productive of any unusual changes

Further examination disclosed that he could recognize objects in the right field of vision perfectly well, but when another object was introduced in the left field of vision the object on the right disappeared Moreover, a quadrantic difference existed If the initial object was within the right superior quadrant, it often became blurred or obscured rather than disappearing If stimulation of the left field was strong, such as that with an intense light, the object in the right field disappeared completely However, it returned within two to four seconds after the stimulation on the left was discontinued If the object was in the right inferior quadrant of vision and stimulation of the left field was begun, it disappeared immediately and reappeared in from five to twenty seconds, the period of lag depending inversely on the strength of the stimulus The same phenomenon occurred when either one or both eyes were tested

Furthermore, if an object was in the right inferior field of vision and the right superior field was stimulated, the object in the right inferior field disappeared or became obscure, the determining factor being the strength of the second stimulus

When colored test objects were used, the fading of color to gray in the affected fields, as mentioned in Bender's case, could not be elicited in this patient Either he recognized the color or it disappeared completely, there being at most a diminution in the intensity or hue The patient could recognize form and contour perfectly Localization in space, ability to fuse objects and stereoscopic vision were also intact Visual imagery and memory were normal After-imagery persisted longer in the left eye than in the right Objects exposed to the right field of vision for less than a second were not recognized If a strong light was present in the left field of vision, it often took him as long as four seconds to recognize an object on the right

Prolonged fixation on the center of a white cross produced no change in the color of the arms of the cross but gave the illusion that the horizontal arm of the cross in the right field of vision became dull The latter change, however, was never sufficient for him to identify the color as gray

In writing columns of figures, the patient tended to displace the columns toward the left When his attention was called to this phenomenon, he wrote in a straight line, but as soon as his attention relaxed the column again tended toward the left side of the page

All psychologic tests were performed most satisfactorily, and no defects could be discovered except that he could no longer do simple algebraic equations, though he had done well in algebra in college Complicated arithmetical problems were performed satisfactorily However, he stated that he was slower than previously Apropos of these observations, the patient volunteered that algebraic symbols seemed to have lost their meaning to him, though, surprisingly enough, there was no other symbolic impairment

CASE 2.—A 27 year old soldier in combat was struck by shell fragments in the right parietal region He was transported to a rear echelon installation, where on admission he was found to be in stupor and had left hemiplegia

Roentgenographic examination at this time revealed a "punched-out, debrided fracture in the posterosuperior portion of the right parietal bone, measuring 5 by 7 cm There were some intracranial fragments of bone, as well as an intracranial metallic fragment, 5 by 18 mm, just behind and within the posterior margin of the defect" On the twenty-second day after injury a cranioplasty was performed The fragments of bone and metal were removed, and a tantalum plate was used to repair the defect in the skull

Examination four months after the injury showed that he was right handed and right eyed Neurologic examination revealed the following condition on the left side The patient had the typical spastic gait of hemiplegia About 50 per cent of normal strength was present, though the face was hardly involved at all There was plastic rigidity of the arm and leg No clinical evidence of atrophy or tenderness was present Pseudoathetoid movements of the arm and fingers were noted, marked ataxia and dysdiadokokinesis were present The deep reflexes were more active on this side than on the right Chaddock and Hoffmann signs were present Light touch sense was intact everywhere Hemihypalgesia was present, being most noticeable in the fingers and toes, with pronounced hyperpathia in the toes Pinprick here provoked a withdrawal response The patient complained that it felt as though the needle were "digging in" At other times he complained that a single pinprick felt as though a "shower of needles" were hitting his foot

Appreciation of vibration was absent distally in both the upper and the lower extremity Appreciation of position was absent, even in the larger joints on the left side Two point discrimination and stereognosis were lost in the left hand, he did not appreciate skin writing on the left hand or foot Tactual localization was inaccurate Examination of the cranial nerves, including the fundi, showed a normal condition Incomplete left homonymous hemianopsia was present In the intact left homonymous superior sector a visual suppression phenomenon could easily be elicited, an object here disappeared when a similar object was placed in the right field of vision

There was left nerve deafness only for the upper tone range On first examination an auditory suppression phenomenon was thought to be present While listening to a tuning fork with the left ear, he stated that his hearing on the left disappeared if a tuning fork was brought close to the right ear Careful checking with an audiometer revealed that attention was the major factor, for the side receiving the second (new) stimulus seemed to be the only side being stimulated It was possible with the audiometer to demonstrate auditory suppression on either side by stimulating the contralateral side

Throughout all the sensory tests there was occasionally a latent period of one-half to three seconds from the moment the left side was stimulated to the

perception of the stimulus regardless of the type of stimulus This initial latency was most pronounced in the foot and least in the face

A true suppression phenomenon was obtained in the cutaneous sensory fields by means of double stimulation If one stroked his left foot, he perceived it clearly If while this stroking continued his right foot was stimulated, sensory perception from the left foot would disappear in two or three seconds If the stimulation of the right foot was discontinued while it was continued on the left, sensory perception returned after a delay of from five to forty seconds The duration of the lag depended on the strength of the stimulus on the right side The same phenomenon occurred for heat, cold and pinprick, but the lag in sensation was not nearly as great as for rubbing

If the left hand was stroked, sensation disappeared when similar stroking of the right hand was begun The disappearance of sensation in the left hand occurred from one to two seconds after initiation of stimulation of the right hand After discontinuation of the stimulation on the right side and continuation of stimulation on the left, sensation would return to the left hand in from two to fifteen seconds Again, the lag depended on the strength of stimulus applied to the right Similarly, if the right side of the face was stroked, with concomitant stroking of the left side of the face, the sensation would disappear promptly from the left side in one or two seconds and would reappear within a second or two after the stimulation of the right side of the face had been discontinued At times, however, the sensation diminished rather than disappeared

Not only was this suppression of cutaneous sensation effected by contralateral stimulation, but it was elicited on homolateral stimulation A gradient appeared as follows If the left foot was stroked, sensation was perceived as usual If, then, the left hand was stroked, sensation from the left foot either became diminished or disappeared entirely within two to five seconds, the determining factor being the strength of stimulus applied to the hand The return of sensation to the left foot on discontinuance of stimulation to the left hand occurred in two to five seconds Similarly, stroking of the left side of the face caused disappearance of the perception of the sensation in either the left hand or the left foot, but this time the effect occurred within two seconds after discontinuation of stimulation to the face At times, however, especially if the stimulus to the face was very light, there was no diminution of sensation in the hand or foot However, if the stimulation of the left side of the face was prolonged and strong, secondary stimulation of the left hand or foot would not be perceived at all

A check on the observations here described was made by initiating sensation on the right side of the body, with the following results When the right foot was stroked continuously and then stroking of the left foot was begun, the initial strokes on the left foot were perceived and promptly identified by the patient However, after two to ten seconds of double stimulation the sensation of stimulation began to fade on the left side and then disappeared The disappearance persisted only so long as the right side continued to be stimulated, and sensation reappeared in two to ten seconds after discontinuation of the stimulation on the right In like manner, if continuous stimulation of the right side of the face was begun and then the left hand or the left side of the face was stimulated, the stimulus to the left hand or to the left side of the face was perceived immediately but faded within a few seconds The strength of stimulus was the determining factor in whether the sensation in the hand disappeared completely or not The table presents the results of the various tests

In all these experiments the stimulus of rubbing the skin was found most amenable to testing and timing The phenomenon could also be elicited from other parts of the body, including the trunk, but heavier stimuli were necessary In all the tests it was impossible to avoid summation effects Single stimuli did not satisfy the conditions for testing

Six months after the injury, the soldier was walking without the aid of a cane, his power had increased, and position sense had returned to the large joints but not to the fingers or toes The phenomenon of visual suppression had disappeared completely and could not be elicited However, the phenomenon of sensory cutaneous suppression could be elicited without difficulty

Electroencephalographic tracings were obtained five and six months after the injury These showed a fairly regular, 11 per second rhythm in the left hemisphere The right hemisphere showed lower voltage in the temporal lead and irregular activity in the occipital lead There was no evidence of epileptogenic foci and no change on hyperventilating Numerous experiments were made with both monopolar and bipolar leads in an attempt to find electroencephalographic changes during the suppression phenomena, and none were found

Timing of Cutaneous Suppression Phenomena *

	Continuous Stimulation of Left Side					
	Left Foot		Left Hand		Left Side of Face	
	D †	R †	D †	R †	D †	R †
Secondary stimulation of right (contralateral) side						
Right foot	2 3	5 40	2 8	2 10	2 8	1 2
Right hand	2 5	5 20	1 2	2 15	2 5	1 2
Right side of face	2 8	2 20	2 5	2 15	1 2	1 2
Secondary stimulation of left (homolateral) side						
Left foot			‡	‡	‡	‡
Left hand	2 5	2 5			‡	‡
Left side of face	0 2	2 5	0 2	0 2		

* The region first stimulated is indicated in the horizontal row, the region secondarily stimulated is indicated in the vertical column

† D indicates time, in seconds, required for disappearance of perception in the first areas stimulated after stimulation of the second (suppressing) zone is begun R, time, in seconds, of reappearance of perception in the first area after the suppressing stimulation is discontinued

‡ In the secondarily stimulated zone the stimulus is perceived, and perception then fades in two to ten seconds under the suppressing influence of the less damaged zone

Speculatively, following the work of Dusser de Barenne and associates,[5] von Bonin and associates,[6] Garol[7] and others who demonstrated the presence of "suppressor strips" in the sensory cortex, one might expect to find during the suppression phenomenon noted in this case a suppression of the electroencephalographic activity over the

5 Dusser de Barenne, J G , Garol, H W , and McCulloch, W S Physiological Neuronography of the Corticostriatal Connections, A Research Nerv & Ment Dis, Proc **21** 246-266, 1941

6 von Bonin, G , Garol, H W , and McCulloch, W S The Functional Organization of the Occipital Lobe, Biol Symposia **7** 165, 1942

7 Garol, H W The Functional Organization of the Sensory Cortex of the Cat, J Neuropath & Exper Neurol **1** 320-329, 1942

sensory cortex Several possibilities are offered in explanation of why such a suppression was not obtained It is likely that the electroencephalographic changes which did accompany the phenomena occurred in such a small area that they could not be picked up with available apparatus Moreover, the presence of the large tantalum plate may have been an additional factor by increasing the area from which the cortical activity was being picked up, thus furnishing too large an area for translation of a suppression phenomenon occurring in a smaller focus

COMMENT

The clinical phenomenon observed in these 2 cases is manifest as a diminution of sensory perception, with gradations from a slight diminution to complete disappearance Previously this syndrome has been called an "extinction phenomenon," clinically a partially adequate descriptive term, herein it is preferred to call it a "suppression phenomenon" In doing so, the hypothesis is offered that the eventual explanation of the syndrome may be correlated with "suppressor strips," already described by neurophysiologists No clinical evidence for support of the hypothesis is present, yet Garol[8] defended the thesis on theoretic grounds These cases certainly corroborate the contention of Bender and Furlow that the phenomenon cannot be wholly explained on the basis of attention Moreover, the evidence from double stimulation of the homolateral field in these cases indicates that cerebral rivalry cannot in itself be considered a complete explanation either The phenomenon is undoubtedly a very complex one The evidence from the cases here presented seems to point toward a primary and basic dependence on a physiologic suppressor action exerted by normal or less damaged tissue, when stimulated, over a damaged sensory cortex There is some reason to believe that the dynamic concept of utilization of energy is a tenable one and that in some unknown way the damage makes it possible for a healthy tissue to use up all available energy, leaving less or no available energy for the damaged sensory cortex From the review of all the cases so far reported, a definite impression exists that a lesion in the parietal lobe, or, probably more specifically, a lesion in parietal association fibers, is part of the underlying pathologic substratum of the syndrome

It is interesting, and perhaps not entirely too far afield, to speculate on the possibility that the phenomenon of attention itself may in some way have a physiologic basis dependent on the function of the parietal lobe The clue to this speculation lies in the details of the reported cases, in which attention directed toward a sensory perception could

8 Garol, H W Personal communication to the author

influence that perception to a greater degree whenever that stimulus was functionally connected with a damaged area

An interesting clinical feature must be stressed Primary stimulation of the normal side did not prevent the preception of stimuli on the damaged side The suppression effect, however, went into operation a few seconds after the secondary perception was initiated This illustrates the well known normal experience of a new stimulus taking precedence over an older one and emphasizes how attention is a factor, though a minor one, in the suppression phenomenon

Another outstanding point is that in the present cases there seems to be clearcut evidence that the suppression phenomenon not only can be exerted by healthy cortex of one side over diseased cortex on the other but may be exerted homolaterally by less damaged tissue over more damaged tissue The latter phenomenon is quite in keeping with the experimental observations of neurophysiologists[9] who have shown that suppressor strips exert homolateral, as well as contralateral, influence

The history in 1 of the cases here presented illustrates that even though visual fields for form and color are normal after an injury one may be missing the reason for continued visual complaints after head injury unless one tests specifically for suppression How frequently the suppression phenomenon exists after a transient hemianopsia is unknown, but my impression is that it is much more frequent than has been recorded previously

CONCLUSION

Clinical studies on suppression phenomenon are reported in which stimuli originating in a normal, or relatively normal, sensory field tended to inhibit or abolish the perception of stimuli arising from an "affected" field

When this phenomenon involves vision, in the presence of normal visual acuity and normal perimetric fields, it may be mistaken for a post-traumatic neurotic reaction The mechanisms underlying the pathophysiologic changes are discussed, emphasis being placed on the fact that the phenomenon may be elicited not only by contralateral but by homolateral stimuli Theoretic implications of the phenomenon are mentioned

74 Perry Street, New York 14

9 Dusser de Barenne, Garol and McCulloch[5] von Bonin, Garol and McCulloch[6] Garol[7]

BILATERAL CONGENITAL ARTERIOVENOUS COMMUNICATIONS (ANEURYSM) OF THE CEREBRAL VESSELS

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CEREBRAL arteriovenous aneurysms have frequently been recorded in the literature However, prior to the brief account of this case [1] the occurrence of bilateral cerebral arteriovenous communications had not been reported A more detailed description of this case, amplified with illustrations and photographs, seems desirable at this time, in the light of the disclosure at operation and necropsy of a second case by one of us (R J) reported in the ARCHIVES by Alpers and Forster,[2] and 2 similar cases described by Russell and Nevin [3] The case here reported is also of unusual interest because of the prolonged period of observation and the opportunity for thorough study at frequent intervals from birth until death, at the age of 4½ years

REPORT OF A CASE [4]

S K, a male infant weighing 9½ pounds (4,310 Gm), was delivered with difficulty by forceps Respiration began immediately, but about two minutes later he collapsed, ceased breathing, became cyanotic and was revived with difficulty The pregnancy had been abnormal in that the mother had continued to menstruate In an examination at term, Dr Walter Reed, of Boulder, Colo , the attending physician, noted that the head seemed abnormally large A roentgenologic examination of the mother's pelvis confirmed this impression and also showed that the

† Dr Forbes died Nov 8, 1943

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1 Jaeger, J R , Forbes, R P , and Dandy, W E Bilateral Congenital Cerebral Arteriovenous Communication Aneurysm, Tr Am Neurol A **63**:173, 1937

2 Alpers, B J , and Forster, F F Arteriovenous Aneurysm of Great Cerebral Vein and Arteries of Circle of Willis, Arch Neurol & Psychiat **54** 181 (Sept) 1945

3 Russell, D S , and Nevin, S Aneurysm of the Great Vein of Galen Causing Internal Hydrocephalus Report of Two Cases, J Path & Bact **51** 375, 1940

4 Dr Walter Dandy, who recently died, and Mrs Dorcas Hager Padget, of Johns Hopkins Hospital, Baltimore, gave invaluable assistance in the study of the specimen in this case All the drawings were made by Mrs Padget

bones of the infant's skull were thicker than normal Two previous pregnancies had been normal, and a boy, 8 years old, and a girl, 6 years old, were living and well The family history was without significance except for congenital heart disease in two cousins

At birth the head was noticeably large, but the fontanels were closed normally There was no heart murmur or other abnormality Breast fed for two months, the infant thrived and continued to gain on a formula Some prominence of the veins of the head was noted during early infancy

Course of Disease—At the age of 8 months the child had a severe attack of "flu" and was ill about eight weeks After this illness he began to have attacks of epistaxis, soon after this a heart murmur was discovered, and it was noted that the area of cardiac dulness was increasing "Fainting spells" also appeared at this time, and he had four or five such episodes, each lasting about five minutes There were no convulsions

At the age of 15 months he was brought to Denver for a pediatric opinion and came under the observation of one of us (R P F) He was large for his age (weight, 26 pounds [11 8 Kg]) The head was large, the bosses were prominent, and a Harrison groove was noted He was exceedingly pale, and the eyes and veins of the face were prominent The heart was symmetrically enlarged about one third above the normal size, according to physical and roentgenologic observations, and a soft, blowing systolic murmur was heard at the base in the third and fourth interspaces The hemoglobin concentration was 55 per cent (Sahli), the red cells numbered 3,950,000 and the white cells 8,750, with a normal differential cell count A diagnosis of congenital heart disease was made, and cod liver oil and iron were prescribed

At 17 months of age he had a second infection of the upper respiratory tract, after which the attacks of epistaxis became frequent and alarming A third infection in the head, at the age of 20 months, was accompanied with uncontrollable nosebleed and acute otitis He was admitted to Childrens Hospital (Denver) after he had fainted, apparently from loss of blood The bleeding failed to stop with nasal packs, and a cautery was used The hemoglobin was 38 per cent (Dare), the red cell count 3,200,000, the blood calcium 11 1 mg per hundred cubic centimeters, the platelet count 195,000, the coagulation time three minutes and the bleeding time one minute The reaction to the Mantoux test was negative, and the electrocardiographic tracing was normal He had two blood transfusions from the mother, receiving 140 and 200 cc The hemoglobin rose to 52 per cent He was discharged in two weeks with a diagnosis of congenital heart disease, rickets and anemia

A month later he was readmitted to the hospital with an acute infection of the left mastoid Operation was performed by Dr Harry L Baum, and the child left the hospital ten days after operation in fair condition, only to return in two weeks because of severe epistaxis The bleeding was controlled promptly with packs, and he was discharged the following day He was taken to California for a month but spent three weeks of the time in a hospital because of severe attacks of epistaxis

At the age of 27 months an infection of the upper respiratory tract was followed by severe nosebleeds, and he was brought to Childrens Hospital for his fourth admission The laboratory reported that the hemoglobin was 35 per cent, the red cell count 2,000,000 and the white cell count 8,100, with 39 per cent polymorphonuclear leukocytes For the first time since he had come under observation a loud bruit was discovered in the neck, being loudest on the left side just below the ear It could not be heard over the cranium The cardiac murmur

was still present, being loudest in the third left interspace, and the heart was enlarged The veins of the face and scalp were prominent, especially before an attack of epistaxis The right angular vein sometimes appeared to be about one-half the size of the small finger The patient could frequently tell the nurses that he was going to have nosebleed five minutes before the attacks began After these attacks he seemed to feel better and the superficial veins were smaller Bleeding occurred every two to six days The shorter the interval the less severe the epistaxis and vice versa Roentgenographic examination showed diffuse thickening of the skull and moderate enlargement of the heart in the transverse

Fig 1—Photograph of patient at 3 years of age Note the enlarged head and dilated veins on the left side of the face and forehead

diameter Some evidence of early healed rickets was visible in the epiphyses of the long bones The blood pressure was 86 systolic and 58 diastolic Lumbar puncture and ophthalmic examination revealed nothing of significance Treatment consisted of two transfusions, of 150 and 125 cc respectively, from the mother The hemoglobin on his discharge after four weeks was 43 per cent (Dare)

At this time it was of course obvious that some defect in the circulatory system of the head was causing the engorgement of the veins, the epistaxis and probably the thickened and enlarged skull An arteriovenous aneurysm was suspected

Within a month the patient was brought back to the hospital because of uncontrollable epistaxis The hemoglobin was 42 per cent (Dare) and the red cell count 2,750,000 Later the hemoglobin dropped to 28 per cent (Dare) He remained in the hospital six weeks and received three intravenous and three intraperitoneal injections of blood, totaling 855 cc The hemoglobin was 44 per cent on his discharge from the hospital

At the age of 3 years the attacks of epistaxis gradually ceased, to be replaced by intermittent headaches and vomiting, which recurred at intervals of several days to three weeks Between attacks the boy's behavior was normal, and he made a gradual gain in weight

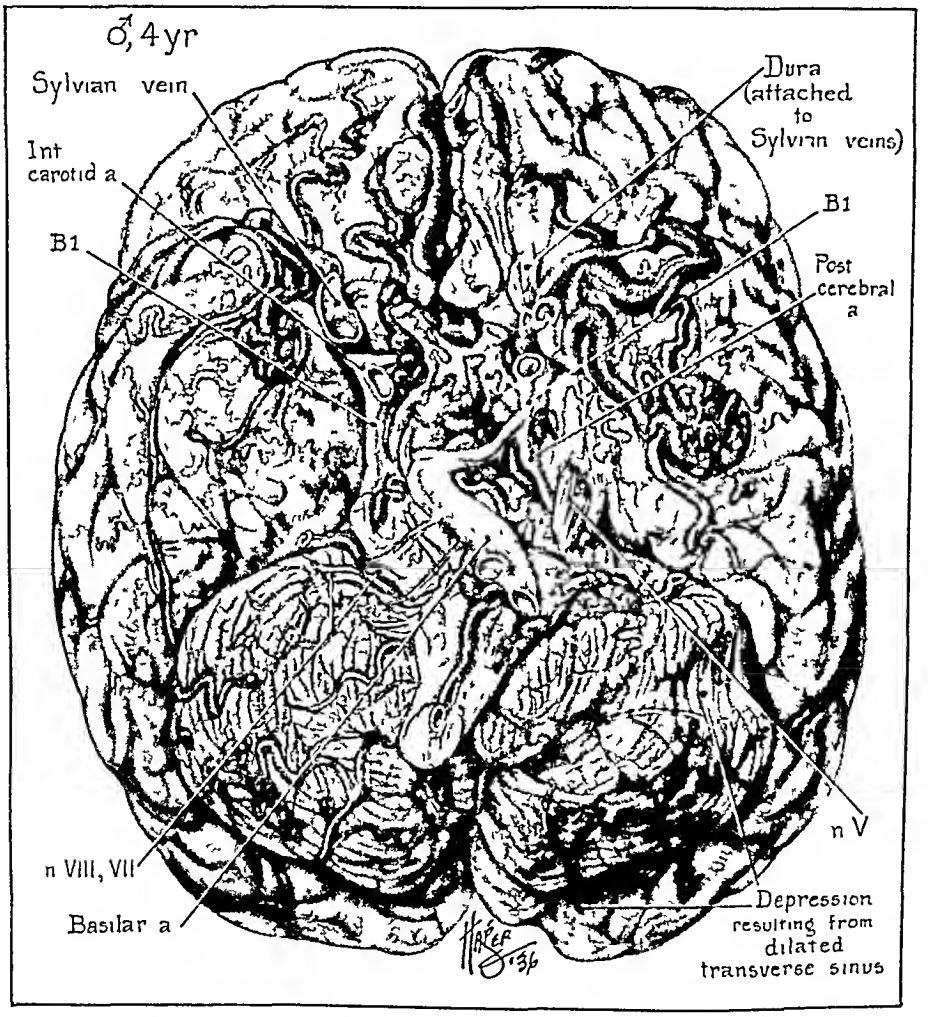

Fig 2—Basal view of the brain, showing the dilated, tortuous veins, which encroach on the cranial nerves and are particularly concentrated at the temporal lobes, from which they drain into the cavernous sinuses All the cerebral arteries are abnormally large, and the circle of Willis exhibits a frequent variation which is a retention of the embryonic condition The posterior communicating arteries (*B 1*, compare diagram, fig 5) are large and directly continuous with the posterior cerebral arteries, so that the latter appear to arise from the internal carotid rather than the basilar artery Each posterior cerebral artery gives rise to an anomalously large artery (representing the posterior choroidal), which empties directly into the internal cerebral veins (Galen)

At 4 years of age his weight was 39 pounds (17 7Kg) and the hemoglobin was 71 per cent (Sahli) The cardiac murmur was very faint Headache and vomiting became a daily occurrence On one occasion the attack lasted two days, and the patient lost sphincteric control and consciousness On his admission to the hospital it was noted that he was weak and had an unsteady gait Neurologic examination showed nothing abnormal except dilated retinal veins No edema or atrophy of the disks was seen Arteriographic studies, made at this time (R J), consisted of exposure of the vessels of the neck on the left side and injection of 5 cc

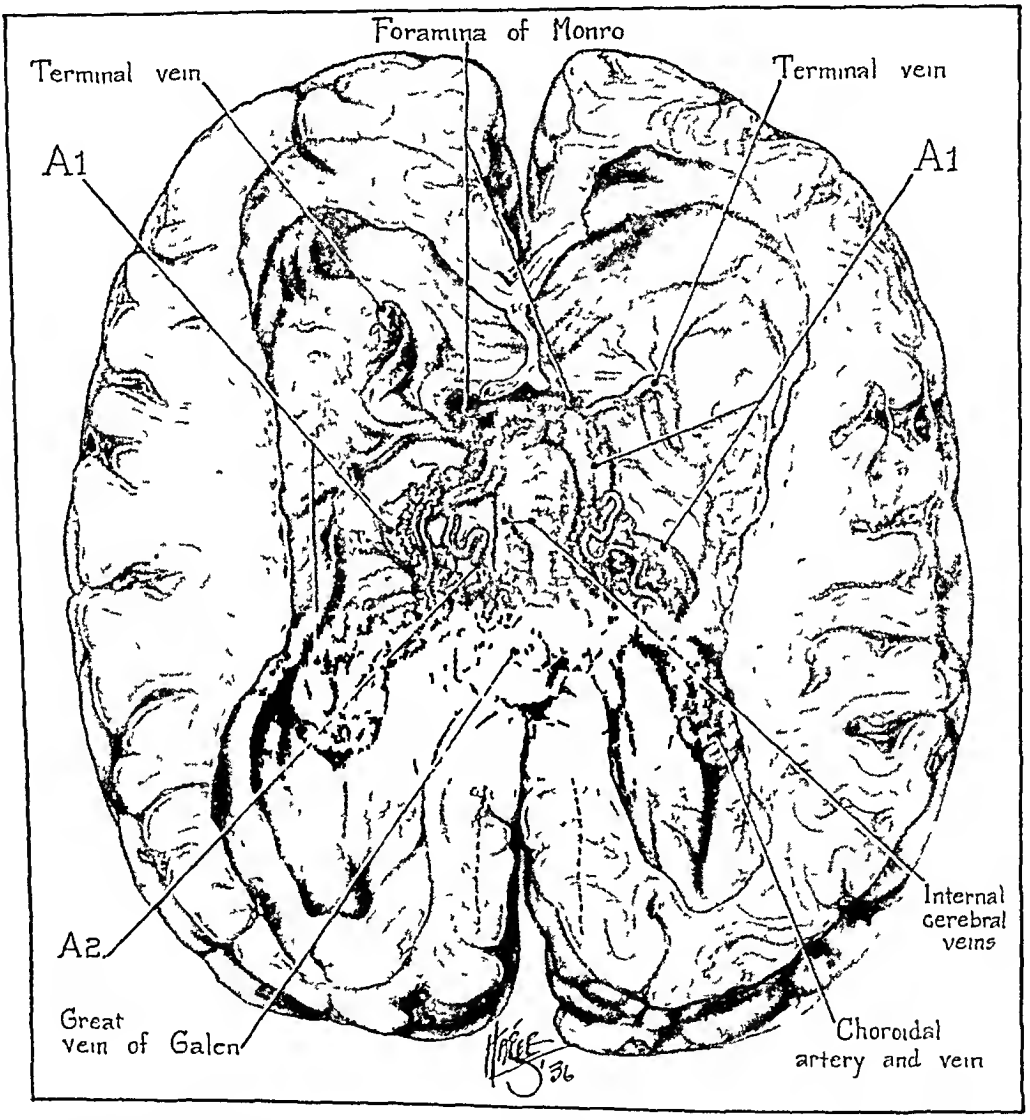

Fig 3—Horizontal section of the hydrocephalic brain, to be compared with the diagram of this view (fig 5) The terminal veins do not enter the internal cerebral veins at the foramen of Monro, as normally, but pass directly into the tremendous sac representing the great vein of Galen Bilateral anomalous vessels, *A1*, arise from the posterior cerebral arteries and empty directly into the dilated internal cerebral veins at the interventricular foramens The smaller anomalous vessel, *A2*, has a similar origin but empties into *A1*

of a 20 per cent solution of sodium iodide into the internal carotid artery Roentgenograms made after injection showed a very tortuous portion of the carotid artery outside the skull and filling of about 1 inch (2 5 cm) of the intracranial portion None of the cerebral arteries was sufficiently filled to be visible, and

no communication between the carotid artery and the venous sinus or the jugular vein was apparent Both the carotid artery and the jugular vein were large, and the jugular vein ballooned out with only slight pressure Other procedures, such as ligation of the common carotid artery and ventriculographic studies, were considered, but the patient was discharged in two weeks, to return later

He was readmitted after two months, with the following history "Since his discharge the patient's condition has progressively been down hill He is no longer able to walk or to get up if on his back He even has difficulty in holding his head up His speech has become unintelligible and his voice weak Spells of vomiting occur once a week and last one day An alternating squint has developed Intelligence is unimpaired The spinal fluid pressure is 200 mm" At this time it was our definite impression that the patient had a cerebral arteriovenous communication, most likely on the left side With this in mind, it was thought best to ligate the left common carotid artery With anesthesia induced with solution of tribromoethanol U S P and ether, the left common carotid artery was ligated The postoperative condition was good He was discharged "unimproved" in three weeks

The patient's eighth, and last, admission to the hospital occurred only three weeks later An infection of the respiratory tract was accompanied with high fever, otitis and swelling in the region of the right parotid gland, and he was in extreme pain Examination of the blood showed 85 per cent hemoglobin (Dare), 4,760,000 red cells and 27,000 white cells, with 82 per cent polymorphonuclear leukocytes The pupils were dilated, there were mild convulsive movements, stupor and increase in temperature to 105 6 F He died fifteen hours after admission

Necropsy—The carotid arteries and the jugular veins were about twice their normal size The carotid arteries were tortuous, and the left one almost looped on itself All the veins in the dura and those of the cortex were greatly enlarged The left jugular vein was three or four times its normal size The entire ventricular system, from the aqueduct up, was dilated This condition was caused by the huge, distended great vein of Galen pressing on the aqueduct This vein was 2 inches (5 cm) long and 1 inch (2 5 cm) in diameter There were a number of anomalous vessels of small size in the vascular arrangement, but the important anomaly consisted in the giving off of large branches from both posterior cerebral arteries to communicate by way of large vessels directly with the small veins of Galen (figs 2, 3, 4 and 5)

COMMENT

Arteriovenous communications are found in all parts of the body but are "most frequently met with about the head" according to Cushing and Bailey[5] The general mechanical arrangement is the same in all, differing only as to the particular anatomic part in which they occur These communications are generally classified according to cause as acquired and congenital Personally, we believe it much clearer to classify them as traumatic, inflammatory and congenital lesions

5 Cushing, H, and Bailey, P Tumors Arising from the Blood Vessels of the Brain Angiomatous Malformations and Hemangioblastomas, Springfield, Ill, Charles C Thomas, Publisher, 1928, p 35

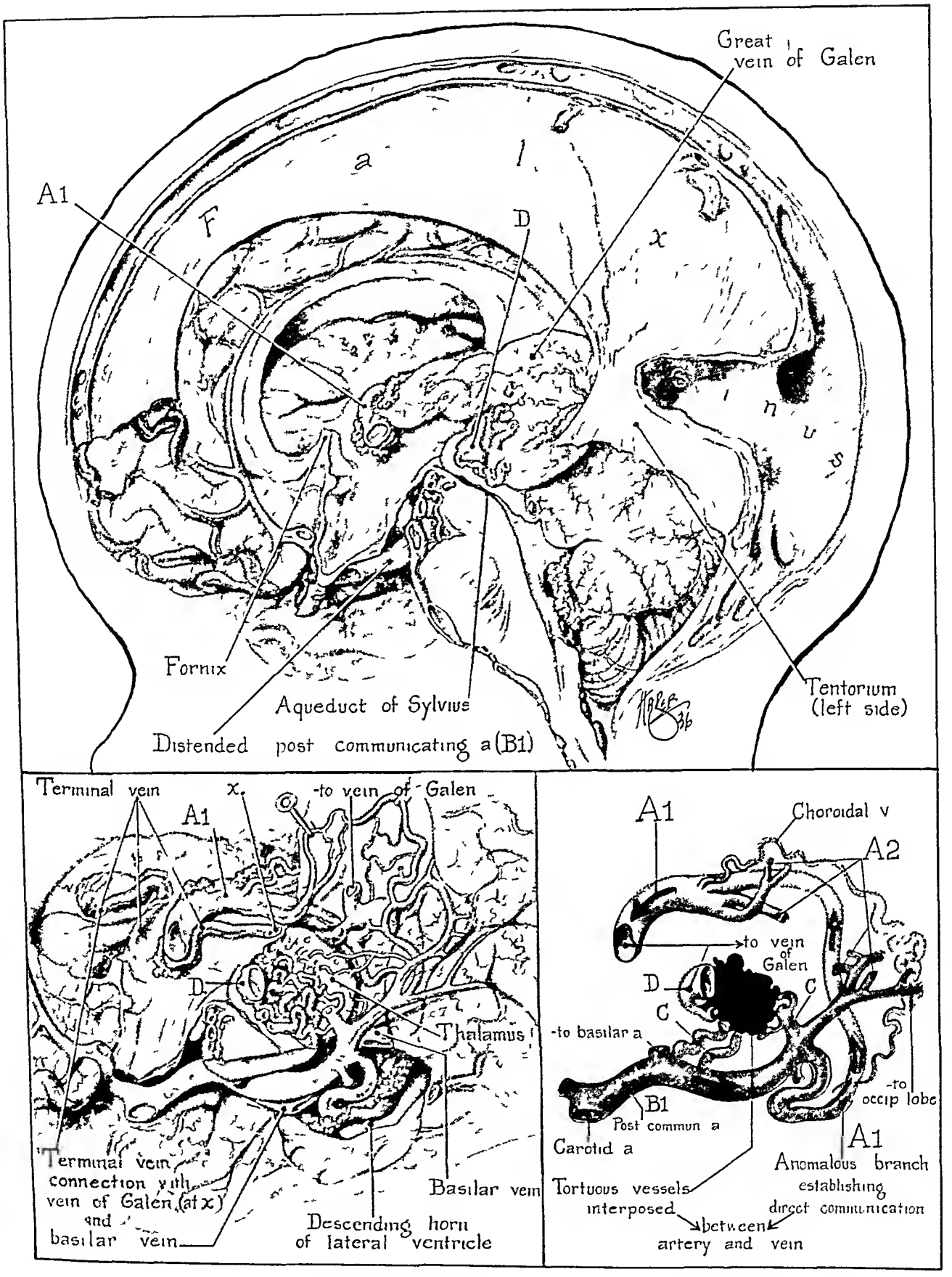

Fig 4—Sagittal section of brain, showing the dilated great vein of Galen producing an intermittent block of the aqueduct The venous sinuses are tremendously enlarged, the torcular Herophili measures 3 5 cm in width and the left transverse sinus about 2 cm As seen in a dissection of this view (lower left) and a simplified diagram (lower right), a dilated vessel, *D*, which empties into the great vein of Galen, drains a coil of vessels excavating the posterior portion of the brain stem and the thalamus This "angioma" is fed by branches (*C*) of the posterior cerebral artery Direct communication between artery and vein is effected by the anomalous branch *A1*, whose proximal end has the origin and course of the normal posterior choroidal artery (arising from the posterior cerebral artery) its upper (distal) end represents the choroidal vein terminating in the internal cerebral vein (Galen) Note that the smaller vessels, *A2*, are also direct arteriovenous connections

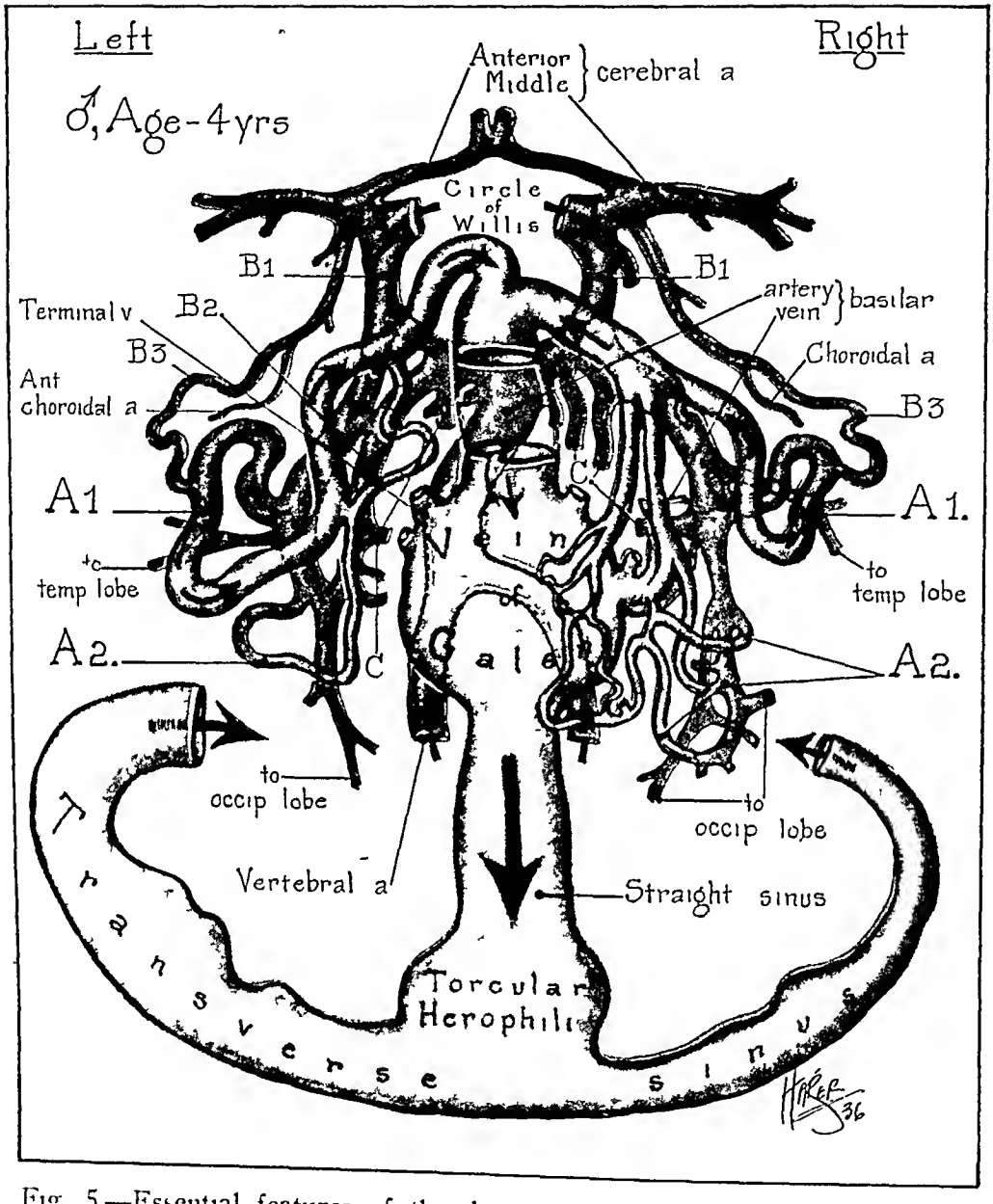

Fig 5—Essential features of the direct arteriovenous connections The coil of vessels interposed between the artery and the vein in the posterior part of the thalamus and brain stem (fig 4) is not included in this diagram, but the arteries feeding it are shown (*C*) *A1* is the bilateral anomalous branch arising in the position of the posterior choroidal artery from the posterior cerebral artery, which is a direct continuation of the dilated posterior communicating artery, *B1* Smaller anomalous vessels, *A2*, pass through the choroid plexus of the lateral ventricle, as do the vessels *A1*, which empty into the divided sac representing the internal cerebral veins Persistence of embryonic features is illustrated by the plexiform or duplicated condition of the left posterior cerebral artery, *B2*, and by the anastomotic branch *B3*, which arises in the position of and gives off the anterior choroidal artery Anastomosis between the anterior and the posterior choroidal artery is a characteristic of embryonic life which is usually retained to a greater or lesser extent in the adult

Traumatic communications are common in cases in which large veins and arteries lie in close apposition and when both are injured by a tearing or cutting object, such as a knife or bullet, and in cases of fracture at the base of the skull in which the internal carotid artery may be torn so as to empty its blood directly into the cavernous sinus

Inflammatory disease may erode the wall of an artery and that of a vein nearby, causing a direct flow of arterial blood into the vein Such erosion is a common lesion of the internal carotid artery as it passes through the cavernous sinus Here it is necessary only for the arterial wall to be eroded as a result of arteriosclerosis or other condition and to rupture into the venous pool surrounding it The infectious type of aneurysm is frequently referred to as mycotic, being caused by circulating micro-organisms lodging in the wall of a vessel

A third, and quite common, cause of abnormal arteriovenous connections is a failure in the development of the capillary bed which normally is interposed between the arterial and the venous system As might be expected, this last type of arteriovenous communication usually differs from the first two in having many large anastomosing channels between the arterial tree and the venous return It is this characteristic when found that identifies it as congenital Several openings between the artery and the vein are sometimes seen in traumatic and inflammatory communications, but never in such numbers as in the congenital type

The present case typifies the usual multiple end-on connections between arteries and veins found with congenital arteriovenous aneurysms and, furthermore, adds evidence in support of the commonly held opinion that they are unquestionably congenital, in that in this case they were found bilaterally in the cerebral hemispheres, arising from both halves of the arterial trees of the circle of Willis Strange to say, as nearly as could be determined by gross dissection, the abnormal anastomoses were largely on the branches of the posterior cerebral artery and its venous return, although anomalous arterial communications were seen to come off the internal carotid artery at the site of the anterior choroidal artery No communications were found to come from the anterior cerebral artery

Another interesting feature of the specimen, in addition to the direct arteriovenous communication through large branches, was the overdevelopment of tiny vascular loops into nests of coiled vessels, which undoubtedly represent anomalous attempts to form a capillary bed between artery and vein This was particularly evident where the posterior cerebral artery gave off branches to a coil of anomalous vessels which lay on the corpora quadrigemina and the thalamus

Here was an attempt at overformation of many small vessels as a substitute for the formation of a capillary bed

On comparing the general anomalous vascular arrangement found in this brain with the observations made by Streeter [6] on the development of the venous system of the brain and with those of Padget [7] on the arterial system, one can see distinctly in this specimen the general outline of the vascular pattern found in the human embryo During the very early stages of fetal development of the circulatory system of the cranial cavity the vascular apparatus is represented by an irregular system of channels which in no way represents the permanent arteries, veins and capillaries From the walls of these primordial vessels sprout endothelial buds which connect with the already established channels, to form arteries, veins and capillaries which gradually take adult form, even long before these vessels have acquired their fully developed histologic structures Midway between the stage of vascular pools without movement of fluid through a definite tubular system and that in which a complete circulatory apparatus of arteries with returning veins is established is a stage which corresponds closely with the pattern found in this specimen One is tempted to conclude that the whole vascular deformity is due to the lack of resistance of a capillary network between arteries and veins, but as yet there is insufficient evidence on which to base any conclusive hypothesis as to what actually determines the malformation Of interest, however, are the detailed observations of Sharrer [8] that in the Placentalia, as exmplified by the monkey, the cerebral veins lie deep to the cerebral arteries This makes it necessary for the veins to cross the arteries at right angles in their course to the dural veins Veins thus are in very close crossed approximation to the arteries The same vascular arrangement is well known in the human embryo Padget in her studies [9] on the embryonic development of the cerebral arteries and veins has noted in some sections a definite denting of the vein by the artery where the artery crosses the vein at a right angle Since the two vessels are separated only by two thin layers of their endothelial walls, the erosion of the artery into the vein, with a resulting direct arteriovenous communication, seems quite possible

6 Streeter, G L The Development Alterations in the Vascular System of the Brain of the Human Embryo, Contrib Embryol **8** 5-38, 1918

7 Padget, D H, in Dandy, W E Intracranial Arterial Aneurysms, Ithaca, N Y, Comstock Publishing Co, Inc 1944, p 70 Contrib Embryol to be published

8 Sharrer, E Arteries and Veins in the Mammalian Brain, Anat Rec **78** 173, 1940

9 Padget, D H Personal communication to the authors

SUMMARY

In this paper is reported a case of bilateral arteriovenous communications of the posterior and middle cerebral arteries observed from birth to the patient's death, at 4½ years of age, with complete necropsy The early symptoms were those of repeated nosebleed Other interesting features of the case were the dilatation and elongation of the veins and arteries with enlargement of the heart Ligation of the left common carotid artery failed to alter the course of the disease, and the patient succumbed to a convulsion several weeks later

It is hoped that the present case report will throw some light on the nature of this lesion and will create an interest in its future detection, so that methods may be devised for its successful treatment

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ARTERIOGRAPHIC VISUALIZATION OF CEREBRO-VASCULAR LESIONS

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CEREBRAL angiography as a method of localizing intracranial lesions was first introduced by Egas Moniz in 1927 [1] After injection of radiopaque substance into the carotid artery, roentgenograms of the cerebrovascular tree were taken Lesions could be identified by their vascular pattern or by the displacement of the cerebral blood vessels Although Egas Moniz strongly advocated the use of his method for the localization of cerebral neoplasms, for the present an insufflation remains the procedure of choice There is agreement, however, that cerebral angiography is a useful technic for the localization of certain vascular lesions,[2] namely, intracranial aneurysm, angiomatous malformations, occlusion of the internal carotid artery and traumatic arteriovenous aneurysm The usefulness of the technic will depend on the proper selection of patients The case histories presented in this report illustrate the use of cerebral arteriography as an aid in neurologic diagnosis

TECHNIC

The technic used was essentially that described by Egas Moniz [3] (1931) After preliminary morphine medication and local procaine anesthesia, a small collar incision was made in the neck and the common or the internal carotid artery exposed After tape was placed about the vessel, 10 to 15 cc of a colloid suspension of thorium dioxide was rapidly injected through a 17 or 18 gage needle into the unoccluded vessel The first roentgenographic exposure to visualize the arteries was made when 10 cc had entered the circulation A second exposure, five seconds later, visualized the venous return Leaking from the artery was easily controlled by pressure after removal of the needle In rare instances a silk suture through the adventitial coat was necessary In our experience, post-

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1 Egas Moniz L'encephalographie arterielle, son importance dans la localisation des tumeurs cerebrales, Rev neurol **2** 72, 1927

2 Elvidge, A R The Cerebral Vessels Studied by Angiography, A Research Nerv & Ment Dis, Proc **18** 110, 1938 Gross, S W Cerebral Arteriography, Arch Neurol & Psychiat **46** 704 (Oct) 1941

3 Egas Moniz Diagnostic des tumeurs cerebrales et epreuve de l'encephalographie arterielle, Paris, Masson & Cie, 1931

operative hemorrhage was never a complication No undesirable reactions were observed after the injection of the thorium dioxide, even though some of the patients were above 60 years of age The patients were allowed to sit up after returning to the ward and were ambulatory the following morning Aside from some aching in the throat on swallowing, they experienced little discomfort Moniz frequently performed this procedure on outpatients, but for the present we have insisted on hospitalization

THE NORMAL ARTERIOGRAM

Although many variations exist in the distribution of the cerebral vessels, the general pattern is more or less similar The following brief description of the gross features of the normal arteriogram (fig 1) is based on the studies of Moniz [3]

Fig 1—The normal arteriogram *E* indicates external carotid artery, *I*, internal carotid artery, *S*, carotid siphon, *P*, posterior communicating artery, continuing as the posterior cerebral artery, *M*, middle cerebral artery, *A*, anterior cerebral artery, *O*, ophthalmic artery, *T*, superficial temporal artery, *F*, transverse facial artery, and *Oc*, occipital artery

The internal carotid artery enters the skull through the carotid canal Coursing ventrally, it passes through the foramen lacerum to enter the cavernous sinus In its course through the cavernous sinus, it describes first a forward and then a backward curve These two together have been termed the carotid siphon On emerging from the sinus, the artery frequently curves forward again to form an S (fig 2) or double carotid siphon A double siphon, more or less complete, occurs in 69 per cent of cases Just before emerging from the cavernous sinus the internal carotid artery gives off the ophthalmic branch

The posterior communicating artery can often be seen branching posteriorly from the terminal end of the internal carotid artery and in 15 per cent of cases continues backward as the posterior cerebral artery Often, as in figure 1, the caliber of the posterior communicating vessel is larger than that of the posterior cerebral artery This substantiates the belief that the posterior cerebral artery, from a developmental viewpoint, should be considered a branch of the internal carotid artery

Of the terminal branches, the middle cerebral vessels are almost always visualized in the normal arteriogram They are frequently displaced upward or downward by mass lesions, and their position is, therefore, of importance in localization of tumors The anterior cerebral vessels, which course medially and anteriorly and then turn backward to outline the curve of the corpus callosum, are less frequently visualized

Although it would seem preferable to make injections into the internal carotid artery and eliminate the branches of the external carotid artery, the visualization of both circulations yields more information The thorium dioxide–blood mixture passes more readily into the cerebral circulation than into the branches of the external carotid artery,[3] so that failure to visualize the former when the external circulation is filled directs attention to an occluded internal carotid artery Not infrequently, as Egas Moniz[4] and Sorgo[5] have demonstrated, the mouth of the internal carotid artery is obstructed in the cervical region, and this lesion could easily be overlooked if the injection were made above the point of obstruction Furthermore, with a little experience, the branches of the two circulations can readily be distinguished We have therefore preferred to make the injection into the common carotid artery

INTRACRANIAL ANEURYSM

The incidence of intracranial aneurysm ranges from 0 5 to 1 6 per cent of routine postmortem examinations of the head[6] Etiologically, these lesions may be classified as mycotic, arteriosclerotic and congenital[7] The mycotic aneurysm, associated with an infected embolus, is apparently rare and was not encountered in the series reported by Globus and Schwab[6a] and by Richardson and Hyland[7] Arteriosclerotic

4 Egas Moniz, Lima, A, and de Lacerda, R Hemiplegies par thrombose de la carotide interne, Presse med **45** 977, 1937

5 Sorgo, W Ueber den durch Gefassprozesse bedingten Verschluss der Art carotis interna, Zentralbl f Neurochir **4** 161, 1939

6 (*a*) Globus, J H, and Schwab, J M Intracranial Aneurysms, J Mt Sinai Hosp **8** 547, 1942 (*b*) Wilson, G, Rupp, C, and Bartle, H, Jr Ruptured Aneurysms of the Circle of Willis, Tr Am Neurol A **68** 140, 1942

7 Richardson, J C, and Hyland, H H Intracranial Aneurysms, Medicine **20** 1, 1941

aneurysm, though more frequent, is relatively uncommon Recent investigators attribute most intracranial aneurysms, variously termed miliary, berry or saccular, to congenital lesions[8] It is generally agreed that syphilis plays little or no role in the formation of intracranial aneurysms The majority occur in the anterior portion of the circle of Willis, 48 per cent involve the internal carotid or the middle cerebral vessel, and 15 per cent, the anterior communicating branch Fifty-four per cent occur in patients over 40 years of age and 35 per cent in patients from 21 to 40[9] years of age

Intracranial aneurysm frequently manifests itself by a subarachoid hemorrhage, with sudden headache, stiffness of the neck and severe pain over the eye or the forehead, with or without loss of consciousness Frequently, there is paralysis of the extraocular muscles, especially those innervated by the third nerve Hyperesthesia in the distribution of the ophthalmic division of the fifth nerve with some diminution in the sensitivity of the corneal reflex may be present Other neighboring nerves may be involved When the hemorrhage extends into the cerebral hemisphere, contralateral hemiparesis, with or without sensory loss or aphasia, occurs Papilledema is rare even when greatly increased intracranial pressure exists, although retinal hemorrhages or unilateral loss of vision may occur

In the following illustrative cases the lesion was visualized by cerebral arteriography

CASE 1.—A white woman aged 20 years first complained of left frontal headaches in August, 1940 and shortly thereafter noticed drooping of the left upper lid On November 10 she suddenly became unconscious On recovery she was unable to speak, the right extremities were paralyzed and the neck was stiff Lumbar puncture, performed at another hospital, showed grossly bloody fluid She slowly regained ability to speak, and the right hemiplegia improved

Examination at the hospital of the University of Pennsylvania on November 30 showed complete ptosis of the left eyelid, with dilatation and fixation of the pupil The eyeball was drawn downward and outward There was no measurable choking of the disk, although the margins appeared hyperemic and blurred Vision, including the peripheral fields, was normal There was right hemiparesis with dysarthria, scanning speech and some difficulty in naming objects The blood pressure was 118 systolic and 96 diastolic Roentgenograms of the skull showed no abnormalities An arteriogram of the left side of the brain showed a small berry aneurysm of the internal carotid artery (fig 2)

Comment.—This case illustrates the typical history of aneurysm of the internal carotid artery, with left frontal headache and paresis of the third nerve at the onset, followed by subarachoid and intracerebral hemorrhage In the arteriogram (fig 2) the aneurysm appears as a

8 Globus and Schwab[6a] Wilson and others[6b] Richardson and Hyland[7]

9 McDonald C A and Korb, M Intracranial Aneurysms, Arch Neurol & Psychiat 42 298 (Aug) 1939

saccular pouch on the posterior surface of the internal carotid artery immediately after its exit from the cavernous sinus The neck of the aneurysm seems constricted, while the caliber of the mass is larger than any of the adjacent vessels According to present concepts, the etiologic factor is a congenital weakness of the wall of the vessel

Case 2.—A white woman aged 46 was admitted to the Hospital of the University of Pennsylvania on Aug 24, 1942 Two months before admission she experienced sudden, severe headache and lost consciousness for forty-eight hours On awakening from the stupor, she was clear and oriented but could not open the right eye At the age of 26 she had had a similar attack, suddenly collapsing on the street with severe headache and inability to see At that time the headache persisted for about a week Her recovery was uneventful and without neurologic sequelae

Fig 2 (case 1).—Aneurysm of the internal carotid artery Note the double carotid siphon

Neurologic examination showed complete palsy of the third nerve on the right side The right eyelid was ptosed, the pupil dilated and fixed to light and in convergence and the eyeball drawn downward and outward The disk in the right eye was obscured by a retinal fold, which seemed pushed forward by a large subhyaloid hemorrhage Several other large retinal hemorrhages were present Other fundal details were obscured In the left eye the disk was normal, the arteries were somewhat attenuated and were irregular, with increased light reflexes and some arteriovenous compression Several large superficial and deep hemorrhages were present throughout the posterior part of the retina Visual acuity was 6/9 in the right eye and 6/22 in the left eye The peripheral fields were full The remainder of the neurologic examination revealed nothing abnormal

The blood pressure ranged from 127 systolic and 90 diastolic to 160 systolic and 110 diastolic The medical consultant expressed the opinion that the patient probably had slight hypertensive heart disease The cerebrospinal fluid pressure

measured 270 mm of water The fluid was clear and contained 20 red blood cells and 15 white blood cells per cubic millimeter The protein content was 35 mg per hundred cubic centimeters Serologic tests of the spinal fluid and blood gave negative reactions Roentgenograms of the skull showed blurring and lack of sharp delineation of the sphenoid ridge on the right side Otherwise the bones of the calvarium appeared normal There was no evidence of increased intracranial pressure The sella turcica was within the limits of normal size An arteriogram of the right side of the brain showed an intracranial aneurysm, probably of the terminal portion of the internal carotid artery (fig 3)

Comment—In this patient, loss of consciousness with palsy of the third nerve followed a mild subarachnoid hemorrhage Although the aneurysm was well outlined, the neighboring cerebral vessels were not clearly shown, making localization difficult The aneurysm appeared to be in the neighborhood of the bifurcation of the internal carotid

Fig 3 (case 2)—Aneurysm, probably at the distal end of the internal carotid artery or the beginning of the anterior cerebral artery

artery, probably along the proximal portion of the anterior cerebral artery The history of severe headache with unconsciousness twenty years previously seems to support the congenital theory of the origin of the lesion and suggests that intracranial aneurysm may remain quiescent for a long interval

Case 3—A Negro aged 48 had complained intermittently of pain over the left eye with left frontal headaches for a year Vision in the left eye had gradually become blurred Three days prior to admission he had noted double vision with inability to open the left eye

Neurologic examination on the day of his admission to the Hospital of the University of Pennsylvania, July 13, 1942, showed complete ptosis of the left upper lid The left pupil was dilated and fixed and did not react to light or in convergence The left eye was turned outward, and external rotation was the

only movement present The fundus was normal The left side of the forehead was hyperalgesic The spinal fluid was bloody and contained 17,600 red blood cells and 28 white blood cells per cubic millimeter The pressure measured 220 mm of water The serologic reactions both of the blood and of the spinal fluid were positive Roentgenograms of the skull were normal An arteriogram of the left side of the brain showed an aneurysm of the internal carotid artery (fig 4)

Comment.—Mild subarachnoid hemorrhage and palsy of the third nerve were the prominent features of this case, although unilateral headache and pain in the eye were premonitory symptoms for a year The use of arteriography would undoubtedly have given an accurate diagnosis prior to the onset of subarachnoid hemorrhage The location of the aneurysm on the posterior aspect of the carotid siphon shortly after the artery emerges from the cavernous sinus resembles that in case 1

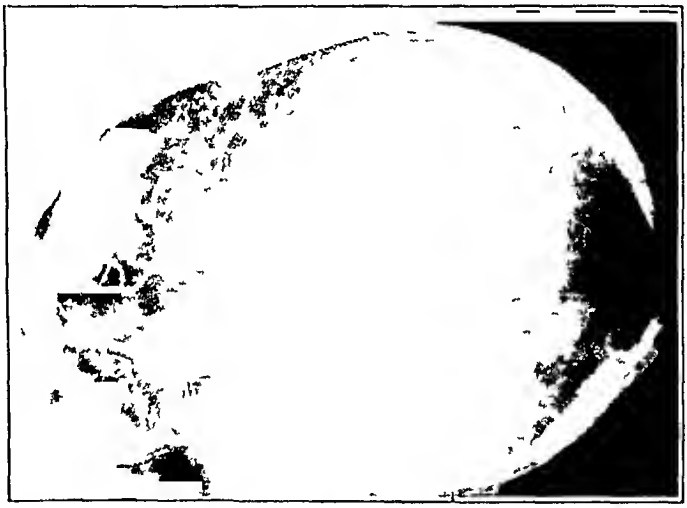

Fig 4 (case 3).—Aneurysm of the internal carotid artery

and, again, suggests a congenital origin Syphilis was probably an incidental discovery and had no relation to the aneurysm

Case 4.—A white woman aged 69 complained of persistent left-sided headaches for five months Intermittent paroxysms of severe pain, confined to the upper two divisions of the left trigeminal nerve, occurred Sometimes the pain radiated into the lower jaw For the past four years diplopia and some drooping of the left eyelid had been noted

Examination on May 1, 1941 showed that the left eye could not be abducted and that the left palpebral fissure was smaller than the right The corneal reflex was diminished on the left side, and the left side of the face was hyperpathic The left optic nerve appeared pale, and there was mild retinal arteriosclerosis Visual acuity was 20/70 in the right eye and 20/200 in the left eye The peripheral field was constricted in the left eye At times a Babinski sign was elicited on the right side The spinal fluid pressure measured 180 mm of water, the fluid was clear and contained 25 mg of protein per hundred cubic centimeters Roentgenograms of the skull showed slight hyperostosis of the inner table of the

frontal bone, a calcified plaque in the falx cerebri and ballooning of the pituitary fossa The dorsum sellae turcica was thin, and the left anterior clinoid process could not be visualized In the basal view, a shadow of increased density on the left of the pituitary fossa was found The left foramen ovale was larger than the right An arteriogram of the left side of the brain showed a large parasellar aneurysm of the internal carotid artery (fig 5)

Comment—This patient presented the syndrome of the cavernous sinus, with paralysis of the left abducens nerve, atrophy of the optic nerve and involvement of the third and fifth cranial nerves There was, in addition, a Babinski sign on the left side, suggesting damage to the pyramidal tract The differential diagnosis lay between neoplasm and aneurysm in the region of the cavernous sinus The arteriogram revealed the nature of the lesion Moreover, it demonstrated that the

Fig 5 (case 4)—Large aneurysm of the cavernous portion of the internal carotid artery Note the loop of the carotid siphon anteriorly

lesion was not a simple saccular or fusiform aneurysm Anteriorly, the outline of the carotid siphon was clearly visible, while the posterior portion had been replaced by a blood-containing mass This suggests that the walls of the artery in this region had become eroded and fused, probably the result of arteriosclerosis

ANGIOMATOUS MALFORMATIONS OF THE BRAIN

Although the term angioma implies neoplasm, this lesion is generally ascribed to a congenital malformation of the cerebral blood vessels Dandy[10] expressed preference for the term arteriovenous

10 Dandy, W E Arteriovenous Aneurysm of the Brain, Arch Surg **17:** 190 (Aug) 1928

aneurysm In Cushing and Bailey's [11] (1928) series of verified intracranial tumors the vascular malformations comprised about 1 per cent of the total Dandy [10] estimated the incidence as 0 5 to 1 per cent of the cases in clinics in which neurologic material is concentrated

The gross appearance of angiomas is striking The lesions consist of large, dilated blood vessels with translucent walls, so that the direction of blood flow and the color of the blood are readily recognized Occasionally, masses of coiled, intertwined arterioles or venules add to the spectacularity of the lesion Histologically, Cushing and Bailey [11] differentiated these lesions from neoplastic growths by the presence of brain tissue between the cords of vessels Although they may occur anywhere in the brain, a large proportion occur in the distribution of the middle cerebral artery Their size is variable, as demonstrated by a comparison of figures 6 and 7 with figure 8

As a rule, the lesion remains quiescent until adult life, in Dandy's [10] series symptoms appeared after the age of 30 in 44 per cent of the cases Ray [12] verified the presence of this lesion in a 2½ year old infant No adequate explanation is available for the delay in the appearance of symptoms The presenting symptom in about one-half the patients is epileptiform seizures, generalized or jacksonian, with or without loss of consciousness The seizures may be preceded or followed by transient sensory or motor paralysis Less frequently the disease manifests itself by an intracranial hemorrhage, with or without paralytic phenomena In a few patients headache may be a prominent symptom Usually there is no choking of the disks Only at times can a head bruit be heard with certainty on auscultation Roentgenograms of the skull generally show accentuated vascular markings, occasionally intracranial calcification is present As Northfield [13] pointed out, air studies are of little aid in diagnosis, although there may be a slight displacement of the ventricles or an ill defined filling defect However, the nature of the lesion is not revealed The electroencephalogram shows no abnormalities unless injury to the cortex results after hemorrhage, as illustrated in case 7 The diagnosis can be made accurately by use of arteriography as illustrated in the following cases

CASE 5.—A white man aged 23 suddenly became extremely dizzy, experienced severe pain over the right side of the forehead and became paralyzed in the left extremities He recalled that he had noted aching over the right frontal region for several days prior to this accident

11 Cushing, H, and Bailey, P Tumors Arising from the Blood Vessels of the Brain, Springfield, Ill, Charles C Thomas, Publisher, 1928

12 Ray, B S Cerebral Arteriovenous Aneurysms, Surg, Gynec & Obst **73** 615, 1941

13 Northfield, D W C Angiomatous Malformations of the Brain, Guy's Hosp Rep **90** 149, 1940

Examination six days later, on May 14, 1941, revealed left spastic hemiplegia with hemianesthesia, moderate stiffness of the neck and an area of paresthesia over the upper two divisions of the right trigeminal nerve No head bruit was audible, vision, including the peripheral fields, was normal, there was no choking of the disks The blood pressure measured 120 systolic and 70 diastolic The cerebrospinal fluid was xanthochromic and contained 238 erythrocytes and 95 monocytes per cubic millimeter The protein content was 175 mg per hundred cubic centimeters The pressure measured 120 mm of water Serologic reactions of the blood and of the spinal fluid were negative Roentgenograms of the skull revealed nothing unusual except for a large venous channel on the right side near the lateral sinus The electroencephalogram showed no abnormalities The arteriogram of the right side of the brain (fig 6) showed a vascular arborization in the right sphenotemporal region, an angiomatous malformation of the brain The arteriogram of the left side revealed an anomalous distribution of the cerebral arteries but no definite congeries of vessels

Fig 6 (case 5) —Angiomatous malformation of the brain in the distribution of the middle cerebral artery

Comment—This case illustrates an angiomatous malformation of the brain, the presenting symptom of which was subarachnoid and intracerebral hemorrhage The history was suggestive of intracranial aneurysm The arteriogram revealed the vascular malformation in the distribution of the middle cerebral artery

Case 6—A white man aged 23 complained of epileptiform seizures For five years the patient had sensations of prickling and numbness, lasting about thirty seconds and occurring three to four times a week These would start in the right foot and spread upward to involve the entire right side In June 1940, after one of these sensory attacks, he suddenly became unconscious and had a right-sided convulsion In the next one and a half years he had seventeen such clonic seizures Recently clumsiness had been noted in the right hand

Neurologic examination, on Dec 1, 1941, showed a normal gait, some impairment of the finer movements of the right hand, normal stereognosis and position sense and some diminution of the protopathic forms of sensation The tendon

reflexes were slightly more active on the right side than on the left, and the strength of the right arm may have been slightly diminished There was an old macular choroiditis with partial atrophy of the left optic nerve and weakness of the right side of the face of central type The cerebrospinal fluid pressure measured 270 mm of water The fluid was clear and colorless and contained 50 mg of protein per hundred cubic centimeters and 6 erythrocytes and 3 monocytes per cubic millimeter Roentgenograms of the skull revealed a localized calcification in the left middle fossa The electroencephalogram showed no abnormalities An air encephalogram showed slight displacement of the midline structures to the right There was no evidence of hydrocephalus or increased intracranial pressure An arteriogram of the left side of the brain (fig 7) showed a large angiomatous malformation, with the internal carotid artery emptying into a large vascular mass deep in the left hemisphere

Comment.—This case illustrates another mode of onset of symptoms of angiomatous malformations of the brain, with jacksonian sensory

Fig 7 (case 6).—Angiomatous malformation of the brain in the distribution of the middle cerebral artery

seizures followed by grand mal attacks The intracranial calcification is characteristic

Case 7.—A white man aged 42 had been well until two and one-half years before At that time he had a sudden attack of severe headache and vomiting Twenty-four hours later numbness and weakness of the left side of the face developed During a month of hospitalization his symptoms gradually cleared, and on his discharge he felt that he had completely recovered Three months later he began to have generalized convulsive seizures, characterized by loss of consciousness, frothing at the mouth and urinary or fecal incontinence, followed by drowsiness These occurred every three to five months but recently had increased in frequency On Feb 2, 1943 he suddenly complained of severe headache and vomited frequently The headache and retching continued for a week, and he was admitted to the Hospital of the University of Pennsylvania

Neurologic examination showed nuchal rigidity, weakness of the right side of the face of central type and hyperactive tendon reflexes in the right lower extremity The remaining cranial nerves were normal The tests for coordination, strength and sensation showed no abnormalities There were no pathologic reflexes The cerebrospinal fluid was xanthochromic and contained 2,430 white blood cells and 13,200 red blood cells per cubic millimeter The pressure measured 580 mm of water The serologic reactions were negative Roentgenographic examination of the skull seemed normal except that the petrous pyramid on the left side was higher and denser than that on the right The electroencephalogram showed a moderate amount of irregularity, most of which appeared in the left frontotemporal lead This consisted of slow, irregular waves with a few sharp, focal spikes The arteriogram of the left side of the brain (fig 8) showed a small angiomatous malformation in the posterior part of the frontal lobe

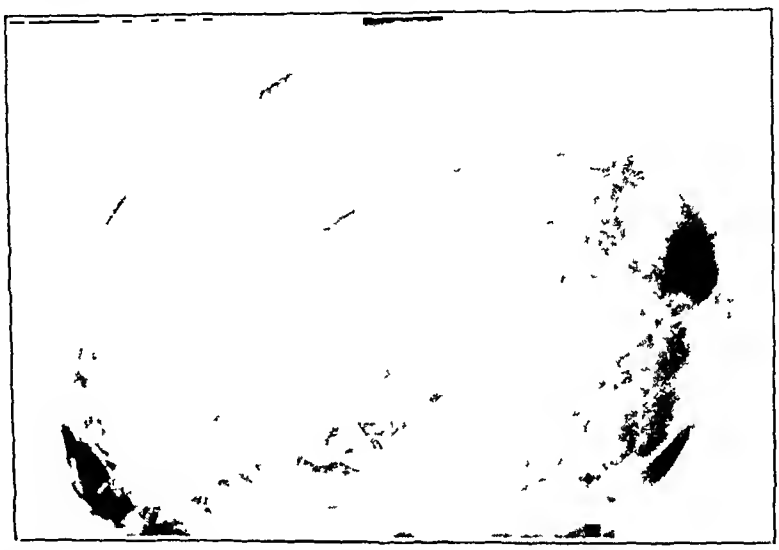

Fig 8 (case 7) —Small angiomatous malformation in the posterior portion of the frontal lobe

Comment—As compared with the lesions in cases 5 and 6, this angioma is small The symptoms of subarachnoid hemorrhage and epilepsy combine the features of the histories in the 2 preceding cases

OCCLUSION OF THE CAROTID ARTERY

Thrombosis of the carotid artery as a source of neurologic disturbance is frequently ignored, both in clinical and in pathologic studies[14] With the advent of arteriography the demonstration of an occlusion either of the cervical or of the intracranial portion of the internal carotid artery has been made with increasing frequency In the few instances in which the occluded vessel has been examined histologically the thrombus has been associated with arteriosclerosis[15]

14 Hunt R The Role of the Carotid Arteries in the Causation of Vascular Lesions of the Brain, Am J M Sc **147** 704, 1914

15 (*a*) Galdston M , Govons, S , Wortis, S B , Steele, J M , and Taylor, H K Thrombosis of the Common Internal and External Carotid Arteries, Arch Int Med **67**·1162 (June) 1941 (*b*) Sorgo

The disease, however, is by no means confined to the elderly Sorgo emphasized that young adults are frequently affected When the common carotid artery is thrombosed, aortic sclerosis or pressure from aortic aneurysm is the most frequent associated lesion Obliterating syphilitic arteritis without aneurysm, embolism, and nonsyphilitic arteritis have been reported in a few instances [15a]

Clinical evidence of occlusion to the circulation of the internal carotid artery is varied and probably depends, as Hunt [14] suggested, on the efficacy of the collateral circulation Symptoms may be absent, and the occluded vessel may be an incidental discovery at autopsy [16] Epileptiform seizures, syncope, mental aberration, unilateral headache or amblyopia may exist independently and without other neurologic disturbance A frequent history is that of transient attacks of hemiparesis progressing to permanent hemiplegia with or without sensory paralysis or aphasia The carotid syndrome of unilateral blindness with contralateral hemiplegia is rarely encountered Roentgenograms of the skull are usually normal, occasionally calcification of the internal carotid artery may be seen Encephalograms generally show some dilatation of the homolateral ventricle without shift of the midline structures The atrophy may be extreme and the entire lobe replaced by a multilocular porencephalic cyst [17] The arteriographic picture is characteristic, the branches of the external carotid artery are filled, the internal carotid artery can be traced to the point of obstruction, and its cerebral branches are not visualized If the patent contralateral vessel is injected in the anteroposterior projection, the vessels supplying both hemispheres can be seen [5]

Case 8.—A white man aged 24, admitted to the Hospital of the University of Pennsylvania on April 15, 1942, complained of "unconscious spells," which dated back to infancy Labor was stated to have been prolonged and delivery accomplished with forceps The left side of the scalp was said to have been severely lacerated The parents stated that he had not been a "blue baby" During infancy, it was frequently noted that his eyes would roll upward and he would appear to be unconscious for several seconds These spells increased in frequency and became more noticeable when the patient was about 6 years of age, he frequently bit the tongue and regularly vomited copious amounts of thick, yellow and green vomitus At the age of 12 it was noted that he usually became stiff and rigid after losing consciousness The rigidity was followed by a period of amnesia and confusion, often by irritability and even aggressiveness No clonic convulsive movements occurred While recovering from the amnesia he often vomited At first these attacks were very irregular, sometimes occurring every two or three days, sometimes not for a month On the average, they

16 Darling, S T, and Clark, H C Arteritis Syphilitica Obliterans, J M Research **32** 1, 1915

17 Erb, W Ein Fall von ausgedehnter Gehirnerweichung bei totaler Obliteration der Carotis communis sinistra, Munchen med Wchnschr **51** 946 1904 Galdston and others [15a]

occurred twice a week In recent years the frequency of the attacks had diminished considerably, and during the past year he had been free of seizures In the month preceding hospitalization the seizures returned and he had two attacks similar to those described

Neurologic examination showed a well developed, slightly asthenic young man, attentive, cooperative and intelligent Except for slight nystagmus on lateral gaze, the cranial nerves were normal Examination of the tendon reflexes, sensation, muscular strength and coordination showed no abnormalities Serologic tests both of the blood and of the cerebrospinal fluid were reported to give negative reactions The cerebrospinal fluid was clear and colorless and contained no cells The pressure was normal Roentgenograms of the skull revealed multiple areas of decalcification localized to the left frontoparietal region There was no evidence of increased intracranial pressure The hypophysial fossa was normal in size and shape An air encephalogram showed moderate dilatation of the lateral ventricles, and the left ventricle was larger than the right The sub-

Fig 9 (case 8) —Occlusion of the internal carotid artery The cerebral vessels are not visualized Note the multiple areas of rarefaction of bone confined to the frontal region

arachnoid channels were all exaggerated The electroencephalogram showed that the alpha rhythm of 7½ per second was moderately persistent and equal on the two sides of the head The general level of activity was normal, but the pattern showed a high degree of irregularity This irregularity took the form of episodes of large waves with a frequency of 3 to 5 per second which appeared to be coming from the left occipital or suboccipital area, with occasional bursts of similar activity on the right side Some of the irregular waves had the classic spike and slow wave form, but the greater part of the activity had the appearance of random irregular waves, among which were a number of large, 3 per second forms The arteriogram of the left side of the brain (fig 9) showed an occlusion of the left internal carotid artery The cerebral vessels were not visualized The branches of the external carotid artery were filled The arteriogram of the right side of the brain seemed normal in the lateral projection

Comment—This case illustrates occlusion of the internal carotid artery, which manifested itself by epileptiform seizures dating back to infancy The unusual presence of multiple areas of rarefaction confined to the frontal area of the affected side is probably related to the birth trauma and is not characteristic of the condition

CASE 9—A white man was first hospitalized on Aug 3, 1938, at the age of 25 He had had severe frontal headaches for two years and thickness of speech for one and a half years In June 1937 he had the first of a series of seizures, in which he suddenly became dizzy, spun to the left and fell to the floor without loss of consciousness Neurologic examination showed slurring and thickness of speech, gross tremor of all extremities on voluntary motion, gross tic of the muscles of the shoulder and back and a shaky, distorted handwriting The cranial nerves were normal The tendon and superficial reflexes were present, and there were no pathologic reflexes Roentgenograms of the skull were normal Serologic and other studies of the spinal fluid showed nothing of significance An air encephalogram revealed that the internal and external air channels were well visualized The air channels about the cerebellum, especially near the cerebellar tonsils, were unusually prominent These observations suggested that the patient had cortical and cerebellar atrophy He was discharged on Aug 22, 1938, with the diagnosis of cerebellar ataxia of undetermined causes

On March 13, 1942, following a bout of severe headache and vomiting, he suddenly became unconscious and was admitted to another hospital Neurologic examination there showed stupor, Babinski and Kernig signs bilaterally and pronounced nuchal rigidity The eyes deviated upward and to the right, and there was hypesthesia over both lower extremities and the left side of the abdomen Lumbar puncture showed grossly bloody cerebrospinal fluid, with a pressure of 225 mm of water The patient improved rapidly and when discharged, a week later, seemed to have recovered completely except for a slight memory defect

On Dec 1, 1942 he had a similar attack of unconsciousness, and on recovery he complained of a pounding sensation in the frontal area and severe diplopia He was admitted to the Hospital of the University of Pennsylvania on December 4 Neurologic examination showed paralysis of the right internal rectus muscle with diplopia on gaze to the left The right pupil was larger than the left, and both reacted promptly to light and in convergence There were nystagmoid jerkings on gaze to the right Dysdiadokokinesis, past pointing and rebound phenomena were present in the right extremities He veered to the right on walking Plantar stimulation showed a Babinski sign on the left and an equivocal response on the right He again improved, and by the time of discharge, on December 11, he had only slight weakness of the right internal rectus muscle The diplopia had cleared There was only a suggestion of cerebellar dysfunction in the right extremities

The patient was referred to the neurosurgical department for cerebral angiographic study on December 26 Except for occasional headache, he had no definite complaints His memory for recent events seemed impaired He was easily annoyed and irritated by trivial happenings The right hand grip was weaker than the left, the patient was, however, left handed Rotary nystagmus could be elicited on gaze to the left The remainder of the neurologic examination revealed nothing unusual Examination of the extremities showed interesting signs There was marked beaking of the finger nails, with clubbing of the distal phalanges There was a splotchy type of cyanosis over the distal portions of both lower extremities The right foot was colder than the left The right

dorsalis pedis artery could not be palpated The right foot blanched more rapidly than the left on elevation and flushed more slowly in the dependent position All the toes were cyanotic in the dependent position The temperature of the skin in response to heat to the forearms did not rise at all, indicating peripheral arterial spasm The remainder of the medical examination, including roentgenographic study of the chest and electrocardiographic recording, showed no significant deviations from the normal The arteriogram of the right side of the brain (fig 10) revealed an occlusion of the right internal carotid artery at the carotid siphon The arteriogram of the left side of the brain seemed normal, although the cerebral vessels appeared somewhat attenuated

Comment—This case presented a puzzling neurologic picture clarified by cerebral angiography The coexistence of peripheral vascular disease and occlusion of the internal carotid artery suggests a cerebral complication of thromboangiitis obliterans, sometimes termed cerebral

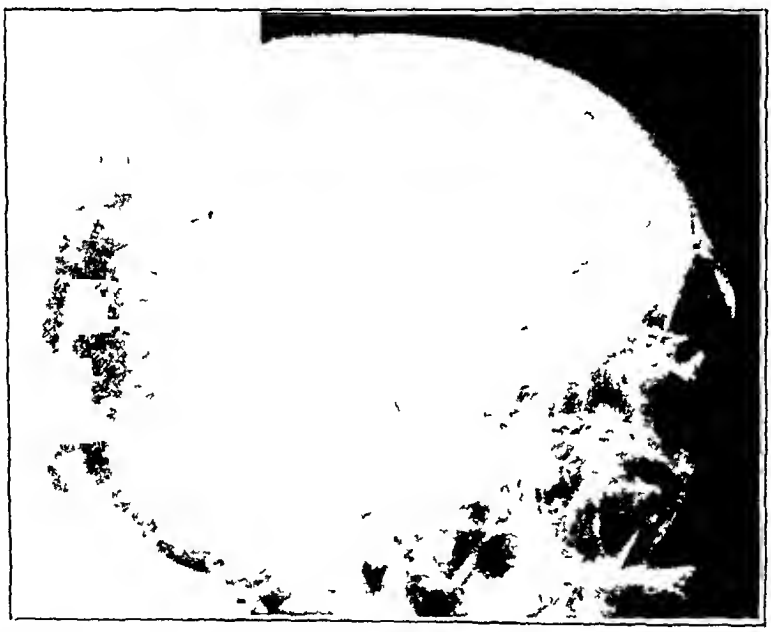

Fig 10 (case 9)—Occlusion of the internal carotid artery The cerebral vessels are not visualized

thromboangiitis obliterans[18] Hausner and Allen[19] found evidence of cerebral involvement in 2 per cent of the cases of peripheral thromboangiitis obliterans

Case 10—A man aged 60, white, complained of transient attacks during which he was speechless and paralyzed in the right extremities These started two months prior to his admission, he had ten such seizures, lasting from ten to fifteen minutes There was no loss of consciousness, he was able to recall conversation and events which occurred during the attack

18 Davis, L, and Perret, G Cerebral Thromboangiitis Obliterans, Quart Bull, Northwestern Univ M School **16** 267, 1942

19 Hausner, E and Allen, E V Cerebrovascular Complications in Thrombo-Angiitis Obliterans, Ann Int Med **12** 845, 1938

Examination on Dec 30, 1940 showed that the patient was well oriented and intelligent There was no evidence of aphasia He walked well, although the right arm did not swing as well as the left There was diminution of strength in the right extremities Sensation was normal The visual fields were full, and the fundi showed mild arteriosclerosis The blood pressure was 106 systolic and 56 diastolic The pulse and respiration rates measured 85 and 17, respectively, per minute Clinical examination of the heart and lungs showed nothing unusual Light pressure over the right carotid sinus (fig 11) produced hyperpnea, pronounced drop in blood pressure, slowing of the pulse to about 40 beats per minute, convulsive twitchings of all extremities and syncope No symptoms were elicited with pressure on the left carotid sinus, although the pulse fell to 60 beats per minute and there was a slight drop in blood pressure The cerebrospinal fluid pressure was normal Electrocardiographic studies and roentgenographic examinations of the chest and skull revealed nothing unusual except for suggestive calcification of the cavernous portion of the left internal carotid artery An arteriogram of the left side of the brain revealed an occlusion of the left internal carotid vessel just proximal to its bifurcation and changes identical with those shown in figures 9 and 10

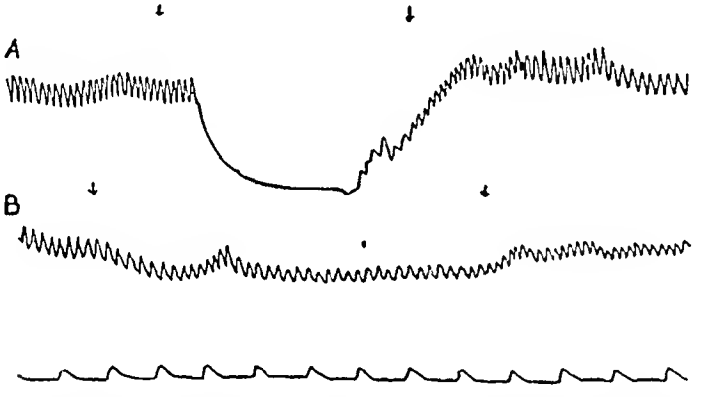

Fig 11 (case 10) —Unilateral sensitivity of the carotid sinus associated with occlusion of the internal carotid artery The intra-arterial blood pressure was recorded by means of a needle in the femoral artery Pressure on the carotid sinus is indicated by the interval between arrows *A* shows recording during pressure on the right carotid sinus, and *B*, recording during pressure on the left carotid sinus The lower line represents the timer recording at five second intervals Syncope and convulsions occurred with pressure on the right carotid sinus Stimulation of the left carotid sinus, on the side of the occlusion, produced no symptoms

Comment —The association of thrombosis of the carotid artery and sensitivity of the contralateral carotid sinus has previously been reported, and it suggested the use of arteriography in this case In the cases reported by Galdston and associates [15a] the occlusion occurred in the common carotid artery, obstructing the carotid sinus region In case 10 the occlusion occurred in the left carotid siphon, and the carotid sinus region was patent In both instances, however, pressure on the right carotid sinus produced syncope, convulsions, slow pulse and pronounced drop in blood pressure, while the left carotid sinus was relatively insensi-

tive The significance of this observation is for the present unknown, although it may have occasional value as a diagnostic sign

TRAUMATIC ARTERIOVENOUS ANEURYSM

The creation of a fistula between the carotid artery and the cavernous sinus is commonly the result of cranial trauma, especially when a basilar fracture of the sphenoid bone occurs The aneurysm is usually unilateral, rarely bilateral, and the symptoms may progress rapidly or slowly The most frequent symptoms are bruit, headache and unilateral pulsating exophthalmos, with diplopia, chemosis and visual disturbances.[20] The following case is illustrative of visualization of the lesion by cerebral arteriography

Fig 12 (case 11) —Arteriovenous communication between the internal carotid artery and the cavernous sinus

Case 11 —A white man aged 34 was unconscious for eight hours after an automobile accident, in December 1942 On recovery, he noticed a whirring noise in the head, present constantly and synchronous with the heart beat On discharge from another hospital, nine days later, he complained of headaches, double vision and spells of dizziness By the middle of April 1943 both eyes became bloodshot and began to bulge, the right more than the left

Examination at the Hospital of the University of Pennsylvania, on June 4, 1942, revealed a head bruit, audible all over the head and without localized intensity Pressure over either common carotid artery stopped the bruit There was moderately prominent exophthalmos on both sides, more marked on the right The conjunctiva was injected in both eyes, with slight chemosis on the right

20 Martin, J D, and Mabon, R Pulsating Exophthalmos, J A M A **121** 330 (Jan 30) 1943

The right pupil was smaller than the left and reacted sluggishly to light The right eye showed limitation in abduction and upward movement There was some limitation of motion in abduction of the left eye Diplopia was present in all fields No pulsation of the eyes could be felt The right disk was blurred but without measurable elevation Hemorrhages and exudates were present about the disk and throughout the posterior portion of the fundus The fundus of the left eye was normal The vision was 6/9 in each eye, and the fields were full The remainder of the neurologic examination revealed nothing abnormal Roentgenograms of the skull showed demineralization of the right half of the dorsum sellae and the right posterior clinoid process An arteriogram of the right side of the brain (fig 12) showed an arteriovenous aneurysm of the cavernous sinus

SUMMARY

Cerebral angiography is an important addition to the armamentarium of the neurologist Intracranial aneurysms, angiomatous malformations of the brain, occlusions of the internal carotid artery and traumatic arteriovenous aneurysms can be accurately localized If full benefit is to be derived from this technic, accurate knowledge of the clinical course of symptoms which these lesions produce is essential Careful evaluation of the history and clinical picture will almost always suggest the presence of the lesion shown in the angiogram

There are, however, several differential points which are associated with these cerebrovascular lesions Alternating syndromes involving the second, third, fifth and sixth cranial nerves with contralateral pyramidal signs are common Transient seizures of varied types are frequent Increased intracranial pressure is generally absent Unilateral sensitivity of the carotid sinus may be suggestive Puzzling neurologic pictures in cases in which air studies are not conclusive may at times be clarified by cerebral angiography Finally, in cases of spontaneous subarachnoid hemorrhage the use of the technic should be seriously considered

Dr E Pendergrass and the staff of the Department of Roentgenology of the Hospital of the University of Pennsylvania gave assistance in making the roentgenographic exposures

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ELECTROENCEPHALOGRAPHIC STUDIES OF PSYCHOPATHIC PERSONALITIES

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PSYCHOPATHIC personalities constitute a large and varied group of personality maladjustments Patients with such disorders suffer from unsatisfactory functioning of self reliance or adjustment to the group in which they live In most cases both unsatisfactory self reliance and group adjustment are present Such personality difficulties cannot be explained by the existence of any of the well defined personality disorders, and at present the psychopathic personality must be considered a separate psychopathologic disorder

Many attempts have been made to classify and explain the psychopathic personality Constitutional dynamic factors are considered essential by some psychiatrists Others believe there is localizable damage to the brain Inheritance has been found to be a definite factor in many cases In recent years psychodynamic factors have been stressed Clinical classifications have been proposed on the basis of various principles A large group of psychiatrists recognize a relation to the classifiable psychiatric illnesses and diagnose as psychopathic personalities patients who show poorly defined features of psychoses and psychoneuroses (e g , schizoid, heboid, cyclic, epileptoid, hysterical and compulsive psychopathic states) This kind of classification is obviously one of convenience Many clinicians stress various types of social difficulties, while only a small number have tried to understand behavior difficulties from a psychopathologic point of view [1]

In the definition and classification presented in this paper, the whole personality as well as outstanding features and reactions were taken into consideration It is an accepted fact that any of the aforementioned etiologic factors may have been present but that such an assumption must be proved in the individual case Psychopathologic reactions must be classified according to fact and reconsidered with new psychiatric orientation

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1 Preu, P W The Concept of Psychopathic Personality, in Hunt, J M Personality and the Behavior Disorders, New York, The Ronald Press Co , 1944

Grouping based on disturbance of function of the personality included disorders of the organization of the personality as well as exaggeration or underdevelopment of personality features Disorders of the organization of the personality may be due to late maturing (immature psychopathic personality) or to a disturbance of the functions which have to do with the synthesis of the personality (loosely organized psychopathic personality) The immature psychopathic personality shows a psychologic immaturity in comparison with his chronologic age Such delayed maturing occurs in adolescents as well as in adults and may be observed especially in the attitude toward life and judgment in general The loosely organized psychopathic personality shows little need and ability for spontaneous adjustment of contradictory strivings and acts Its opposite type is characterized by lack of plasticity, resulting in rigid personality

Disturbances of groups of personality functions lead frequently to psychopathic maladjustments From a practical point of view, personality functions may be subdivided, an artificial and frequently overlapping, but nevertheless useful, procedure The following subdivisions have been postulated (1) intellectual resources, (2) emotional tendencies and temperament, (3) volitional and action tendencies, interests and strivings, (4) standards, (5) attitude toward one's own body and toward the instinctive desires, (6) attitude toward material needs, (7) attitude toward oneself and ability to deal with oneself, and (8) social needs and adjustment to the group In studying psychopathic personalities, one may look for basic disorders in any of these personality functions In the intellectual field, where, by general consensus, insufficient intellectual development (feeblemindedness) is excluded, a type of personality characterized by poor concept formation in the setting of an adequate or high general intelligence can be singled out A large number of patients have difficulties because of insufficient control of excessive emotional reactions In others, lack of persistence in pursuing goals, vacillation and a discrepancy between ambition and ability are outstanding Inadequate standards lead to antisocial and asocial acts Difficulty in controlling instinctive desires is found to be of paramount importance in many sexual perversions Insufficient self reliance and general inadequacy characterize another type In many patients there is primarily a disturbance in the attitude and reactions to the group, a lack of belonging and of the need to share with others

When the many possibilities of psychopathic maladjustment are considered, it becomes obvious that further advances can be made if each patient is studied from a psychobiologic point of view, genetic-dynamic, as well as constitutional, factors being accepted The mere presence of psychoneurotic reactions does not necessarily explain the whole disorder on a psychoneurotic basis, nor does the presence of

constitutional factors, or a special type of heredity, force one to accept a constitutional cause [2]

COMBINED ELECTROENCEPHALOGRAPHIC AND PSYCHOPATHOLOGIC STUDIES

In the course of routine electroencephalographic examinations of selected patients in the Payne Whitney Psychiatric Clinic, 69 psychopathic personalities were investigated The electroencephalographic interpretations were made by one of us (D J S) without knowledge of the clinical picture Records were taken by means of a two channel ink-writing oscillograph of the Grass type, using symmetrically placed bilateral electrodes from the frontal, parietal and occipital regions and the ear lobes Two minute monopolar and bipolar records were made Overbreathing was carried out for four minutes Some of the patients were given 100 Gm of dextrose by mouth before the test was made in order to eliminate the possibility of slow waves due to low blood sugar In a few patients the blood sugar level was determined, and the results suggest that probably all the patients had a blood sugar content above 100 mg per hundred cubic centimeters at the time of the test (In every case the fasting blood sugar had been determined a few days before the test and was never found to be below 90 mg per hundred cubic centimeters) General physical and neurologic examinations were made All the patients were in good physical health The psychopathologic study was carried out during a period of one to several months while the patient was in the hospital and consisted of observations on behavior, personality analysis and special psychologic tests Detailed histories were obtained from patients and relatives and from other sources whenever indicated

The following psychopathologic patterns emerged

A Psychopathic personalities definitely of a psychoneurotic type

The 12 patients of this type exhibited social maladjustment of such a degree that the diagnosis of psychopathic personality seemed indicated Some of these patients presented psychoneurotic symptoms, but the total psychopathologic picture was not that of a well defined psychoneurosis The characteristic feature was an inability to adjust to the realities of life Any of the previously discussed pathologic personality reactions might be observed Their recognizable onset was in childhood or early adolescence, and in only a few patients in the latter part of adolescence

All these patients had normal electroencephalograms

B Psychopathic personalities of cyclothymic type

The outstanding feature in the 7 patients of this type was their pronounced and easily provoked mood swings, which made a successful life impossible These mood reactions occurred with such frequency as to lead to chronic maladjustment Many of these patients utilized psychoneurotic factors with these emotional reactions

All these patients had normal electroencephalograms

2 Diethelm, O Basic Considerations of the Concept of Psychopathic Personality, in Seliger, R V, and Lindner, R M Handbook of Correctional Medicine, to be published

C Psychopathic personalities with poor ethical standards and resulting social difficulties

Outstanding features were irresponsibility, with disregard of consequences, lack of persistence of emotional relationships and lack of emotional depth [3] Despite good intelligence, these patients were unable to profit from experience The symptoms of their maladjustment were stealing, untruthfulness, truancy and irresponsibility with regard to social and financial obligations All the patients in this group were aggressive

All 11 patients had abnormal electroencephalograms characterized by 5 to 7 a second, moderately slow activity (fig 1)

D Psychopathic personalities with loose organization of personality and immaturity

The characteristics were unsatisfactory emotional control, contradictory strivings, poor self discipline and, frequently, a rebellious attitude toward authority and society These patients were of the aggressive as well as of the passive types

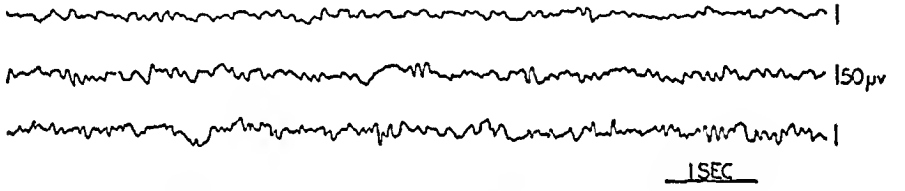

Fig 1—Specimens of the right parietal leads of 3 patients These records exhibit the 5 to 7 a second type of abnormality

The 31 patients of this type who were studied presented a mixed group of electroencephalographic patterns, in which normal, moderately slow and very slow and fast types of activity occurred

E Psychopathic personalities with a generally inadequate type of personality and vague thinking

These patients lacked persistence in pursuing goals, which were frequently poorly defined They had a tendency to blame their inadequacies on external situations and on lack of help from others They expected to be supported by others but had not developed an undue emotional dependence on them Minor psychoneurotic reactions, with anxiety and resentment as the outstanding emotions, occurred readily Some of them had high ethical standards, others, unusually low All were of average or superior intelligence, but they showed difficulty in concept formation and logical thinking They were of the aggressive as well as of the passive types There were 8 patients in this group, of whom 5 had low voltage activity slower than 5 to 7 a

3 Greenacre, P Conscience in the Psychopath, Am J Orthopsychiat **15**: 495-509 (July) 1945

second and none had an electroencephalogram which was considered normal (fig 2)

ELECTROENCEPHALOGRAPHIC DATA

Records showing frequencies lower than 8 a second or an abundance of waves slower than 8 a second in the frontal leads, regardless of amplitude, were considered abnormal This is essentially in accordance with the criterion of Gibbs, Gibbs and Lennox [4] The record of 1 patient was considered abnormal during overbreathing only

All the abnormal records fell under the type of electroencephalograms usually called "pathologic record of undetermined type" Fifty-three

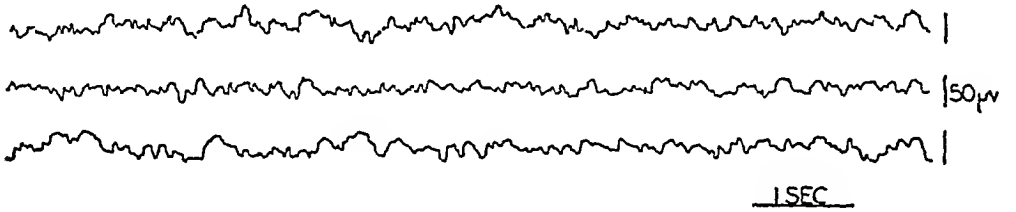

Fig 2—Specimens of the right parietal leads of 3 patients These records exhibit activity which is slower than 5 cycles per second

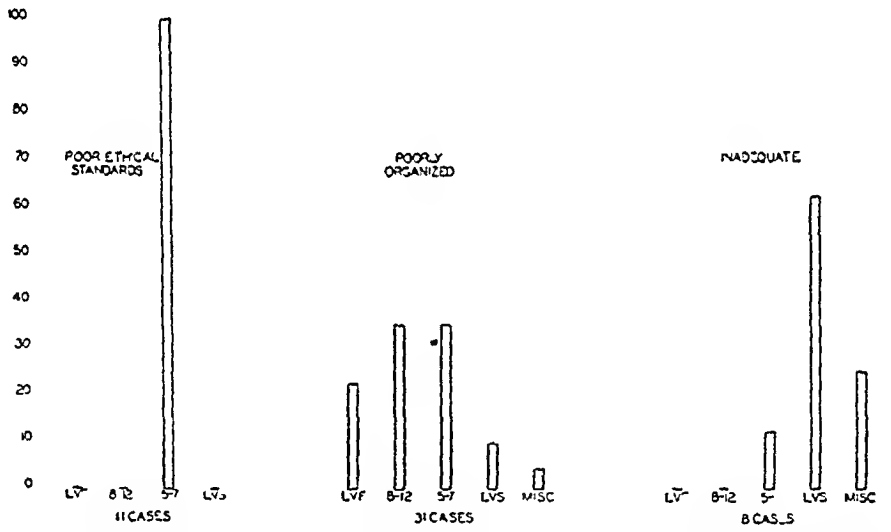

Fig 3—Distribution of electroencephalographic abnormalities among the clinical groups

per cent of the patients had abnormal records It was possible to divide these pathologic records into two types, namely, those of average amplitude, 5 to 7 a second activity, and those of low voltage, slower than 5 to 7 a second activity A third pattern—low voltage, fast activity—was frequently encountered, but it was not considered definitely abnormal

The majority of the abnormal records were those containing sufficient 5 to 7 a second activity of low average amplitude in the frontal

4 Gibbs, F A , Gibbs, E L, and Lennox, W G Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch Neurol & Psychiat 50 111-128 (Aug) 1943

and parietal leads to be considered beyond the limits of normal Some 5 to 7 a second activity is commonly found in the frontal records of normal subjects, but it is unusual in the parietal leads Any considerable amount of it in the frontal and parietal leads must certainly be considered abnormal Figure 1 shows samples of records from the parietal leads of 3 patients with the 5 to 7 a second type with low average amplitude

Figure 2 shows samples of the activity of low average amplitude which was slower than 5 to 7 a second

Figure 3 shows the distribution of electroencephalographic abnormalities among the clinical groups

COMMENT

Hill and Watterson [5] reported that 65 per cent of their 66 "predominantly aggressive psychopaths" and 32 per cent of 38 "predominantly inadequate psychopaths" (Henderson's [6] classification) had abnormal records, while 5 "purely delinquent" persons and 7 of 8 persons with sexual perversion had normal records The most characteristic abnormality in the records of these persons was the occurrence of relatively well formed 4 to 6 a second waves of slightly less than average amplitude occurring in bursts of 3 to 6 waves at a time This is in approximate agreement with our observations

These authors also looked for isolated, random waves with a frequency of 6 per second or less and a voltage equal to or more than that of the dominant rhythm and for series of waves with frequency of 14 a second or more and a voltage rising to over half that of the dominant rhythms They did not mention finding such abnormalities

Their criterion of abnormalities due to overbreathing may be correct, but it is not one which is in general use, namely, "3-cycle smooth waves of high voltage [appearing] either as a continuous series or in bursts of 3-6 at a time [and] their persistence for more than 20 seconds after the cessation of hyperventilation or their re-occurrence after the record has started to return to normal"

Knott and Gottlieb [7] did not differentiate types of psychopathic personality beyond "unspecified [type], [those] with pathologic sexuality, those with pathologic emotionality, [those] with asocial and amoral trends" They considered as abnormal those records showing frequent bursts of rhythmic activity slower than 8 a second and of a voltage

5 Hill, D, and Watterson, D Electro-Encephalographic Studies on Psychopathic Personalities, J Neurol & Psychiat **5** 47-65 (Jan-April) 1942

6 Henderson, D K Psychopathic States, New York, W W Norton & Company, Inc, 1939

7 Knott, J R, and Gottlieb, J S The Electroencephalogram in Psychopathic Personality, Psychosom Med **5** 139-141 (April) 1943

greater than the average voltage of the record, or, if infrequent, protracted bursts of slow activity They considered as questionably abnormal those records which showed repetitive slow waves of low voltage occurring infrequently in short sequences They did not make use of records obtained during or after hyperventilation Fifty-two per cent of their patients had records which were "not normal" It is interesting that so many of their patients with pathologic sexuality had abnormal records (5 out of 7), for other investigators have rarely found electroencephalographic abnormalities among psychopathic personalities with pathologic sexuality

It is difficult to evaluate pathologic sexual activity because this psychopathologic reaction may occur in different types of psychopathic personalities In the group of patients we studied, 2 belonged to the type characterized by poor ethical standards (pathologic electroencephalogram) and 4 to the loosely organized, immature type (pathologic electroencephalogram), their electroencephalographic records corresponded to those of the group mentioned and did not offer a uniform pattern which could be related to pathologic sexual life

In their second paper,[8] in which the Gibbs, Gibbs and Lennox classification was used, Knott and Gottlieb did not distinguish types of psychopathic personality Of the 68 patients reported on there, 55 per cent had abnormal records Twenty-six per cent of their patients were in the 16 to 17 year age group, and 47 per cent were under 22 years old In the present study 36 per cent were in the 30 to 40 year old group.

Silverman[9] classified 75 psychopathic personalities under three types hostile, hedonistic and inadequate Electroencephalograms were classified as normal, borderline and abnormal He designated as abnormal those records which contained frequencies "below 7 5 a second and/or high voltage spike activity in roughly more than 10 per cent of the record" In the borderline group were placed records showing arrhythmia and those showing abnormality only on overbreathing Of his patients, 20 per cent had normal records; 26 6 per cent had borderline records, and 53 4 per cent had abnormal records Of the last group, one-half had definite 6 a second activity in the frontal and prefrontal areas The bulk of his patients were in the 19 to 21 year age group, 45 per cent were between 19 and 24 years of age In contrast to our series, 53 per cent (39) of his subjects had "neurologic signs and/or histories suggestive of a cerebral lesion" Of these 39 patients 80 per cent had doubtful or abnormal records, and 81 per cent of his 36

8 Knott, J R, and Gottlieb, J S Electroencephalographic Evaluation of Psychopathic Personality Correlation with Age, Sex, Family History and Antecedent Illness or Injury, Arch Neurol & Psychiat **52**·515-519 (Dec) 1944

9 Silverman, D Clinical and Electroencephalographic Studies on Criminal Psychopaths, Arch Neurol & Psychiat **50** 18-33 (July) 1943

patients without evidence of disease of the nervous system had doubtful or abnormal records It is noteworthy that Silverman's "material included examples of the most extreme and dangerous criminal psychopathic types" There is no indication that the psychopathic personalities in his series were essentially different from those in ours Their extremely asocial behavior does not necessarily indicate a greater degree of psychopathologic malfunction but may be the result of environmental influences

All patients in the present study were examined from a neurologic point of view, but no defects in function of the nervous system were found There was no evidence of any structural change in the brains of these patients Records obtained from persons with brain tumor, neurosyphilis, some cases of encephalitis and multiple sclerosis usually show patterns of higher amplitude and slower rate than any seen in this group For this reason, also, it cannot be inferred that there were any underlying structural changes in the brains of the persons studied here The abnormalities must be considered a result of some physiologic anomaly

SUMMARY

From our studies it appears that the concept of psychopathic personality can be more clearly defined than it has been previously In a considerable number of psychopathic personalities, distinct clinical pictures can be differentiated Two of the groups with psychopathic personalities had particular types of electroencephalographic abnormalities Those of a third group were not well defined, showing both normal and pathologic patterns

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PHENOMENA OF FLUCTUATION, EXTINCTION AND COMPLETION IN VISUAL PERCEPTION

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OF THE various systems which subserve perception in the primate organism, perhaps none has been better explored than the visual apparatus A good deal of information on the optic pathways has been obtained by the anatomist and the clinician. According to Brouwer and Zeeman,[1] Brouwer[2] and Polıak,[3] the visual fibers originating in the retina follow an orderly path and seem to show throughout a point for point relationship to the occipital cortex However, from the functional standpoint the concept of point for point representation is not altogether tenable Recent physiologic and clinical investigations have revealed that a mechanism such as the "peaking of excitation processes" in widely overlapping neurons provides a better hypothesis for visual function[4] Talbot and Marshall's animal experiments show that this dynamic representation furnishes a closer correspondence between retina and visual cortex than any fiber per fiber relationship could ever yield to the seeing organism

On the other hand, the mass of clinical material on the extent of impairment following circumscript lesions in the geniculocalcarine-

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1 Brouwer, B , and Zeeman, W P Projection of Retina in Primary Optic Neuron in Monkeys, Brain **49** 1-35, 1926

2 Brouwer, B Chiasma, Tractus opticus, Sehstrahlung und Sehrinde, in Bumke, O , and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 6, pp 449-532

3 Polıak, S The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, University of California Publications in Anatomy, Berkeley, University of California Press, 1932, vol 2, A Contribution to the Cerebral Representation of the Retina, J Comp Neurol **57**.541-617, 1933

4 Talbot, S A , and Marshall, W H Neural Mechanisms of Visual Localization, Am J Ophth **24** 1255-1264, 1941 Marshall, W H , and Talbot, S A Recent Evidence for Neural Mechanisms in Vision Leading to a General Theory of Sensory Acuity, Biol Symposia **7** 117-164, 1942

pathway suggests that there is indeed a close correspondence between the amount or locus of fibers which are damaged and the localization and extent of resulting scotomas The closeness of this correspondence has sometimes been questioned with regard to the macular region, but with use of proper procedures so-called macula sparing appears to be either a mere phase in a developing hemianopsia or a sign of readjustment to a defect which actually splits the macular region [5]

Both for practical and for research purposes, the perimeter and the tangent screen are the instruments of choice in defining the locus, extent and density of any scotoma A perimetric examination is admittedly time consuming, but no clinician will forego such examination if a neoplasm is suspected or if the extent of a cerebral injury involving the optic pathway has to be defined

Perimetric measurement thus gives an adequate picture of loss or impairment in anatomic structure But such a field does not unequivocally define how much a patient actually sees [6] Subjectively he may see either more or less than his plotted field would show Objectively, additional changes in visual function might be demonstrated by methods other than perimetric measurement or tangent screen examination

SUBJECTIVE FIELD OF VISION

By the term subjective visual field we mean the vision of which the person is aware and which he describes One of the major factors that make the field experienced by the patient different from the one plotted on the perimeter is the varying degree of awareness of a scotoma which he may have A small plotted scotoma may be so apparent and bothersome to a patient that it can become almost an obsession Conversely, he may be unaware of a large scotoma to such an extent that his attitude may resemble that in the syndrome of denial of blindness, as described by Anton and others [7] Between these two extremes are various gradations of disturbances of awareness It is well known that most patients with hemianopsia eventually are unaware of their defect This has been explained by the fact that the median

5 Bender, M B, and Kanzer, M G Dynamics of Homonymous Hemianopias and Preservation of Central Vision, Brain **62** 404-421, 1939

6 Compare Fuchs's [8] classic distinction between visual field (*Gesichtsfeld*—perimetric field) and field of actual vision (*Sehfeld*—psychologic field)

7 Anton, G Ueber Herderkrankungen des Gehirns, welche vom Patienten selbst nicht wahrgenommen werden, Wien klin Wchnschr **11** 227-229, 1898 Redlich, F C, and Dorsey, J F Denial of Blindness by Patients with Cerebral Disease, Arch Neurol & Psychiat **53** 407-417 (June) 1945 Bender, M B, and Furlow, L T Visual Disturbances Produced by Bilateral Lesions of the Occipital Lobes with Central Scotomas, ibid **53** 165-170 (March) 1945

plane has been shifted and a new center of distinctness, or a "pseudo-fovea," has been formed [8]

The various intermediate degrees of partial awareness of scotomas have been less explored and are somewhat unfamiliar to most examiners Their phenomenology is complicated by the fact that many of the most pronounced displacements and distortions of images occur in defective fields of vision which are in the process of reorganizing themselves around an emerging pseudofovea Thus, a patient may apportion different parts of a homonymous scotoma to each eye For instance, he will maintain that one eye is obscured by a "curtain" shorter than one which apparently covers the other eye, even though perimetric examinations show congruent defects in the homonymous fields

Besides disturbances in awareness, the subjective fields of vision may be characterized by far reaching qualitative changes in perception Such phenomena as monocular diplopia and polyopia,[9] micropsia or macropsia,[10] dysmorphopsia [11] and disturbances in perception of color [12] and of motion [13] could be found in the defective regions of the fields of vision

These disturbances in perception are present much more commonly than has hitherto been reported and must be more than pathologic curiosa Indeed, they seem to reveal certain aspects of the psychologic and physiologic forces which underlie all normal perception, especially for color, space and motion The patient's verbal reports and drawings of what he sees have therefore considerable heuristic value

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8 Fuchs, W · Untersuchungen uber das Sehen der Hemianopiker und Hemiamblyopiker I Verlagerungserscheinungen, Ztschr f Psychol **84** 67-169, 1920, II Die totalisierende Gestaltauffassung, ibid **86** 1-143, 1921

9 Hoff, H, and Potzl, O Zur diagnostischen Bedeutung der Polyopie bei Tumoren des Occipitalhirnes, Ztschr f d ges Neurol u Psychiat **152**.433-450, 1935

10 Gelb, A, and Goldstein, K Zur Frage der gegenseitigen funktionellen Beziehung der geschadigten Sehsphare bei Hemianopsie (Mikropsie infolge der Vorherrschaft der Vorgange in der geschadigten Sehsphare), Psychol Forsch **6** 187-199, 1925

11 Gelb, A Ueber eine eigenartige Sehstorung ("Dysmorphopsie") infolge von Gesichtsfeldeinschrankung Ein Beitrag zu der Lehre von den Beziehungen zwischen "Gesichtsfeld" und "Sehen," Psychol Forsch **4** 38-63, 1923

12 Gelb, A Ueber den Wegfall der Wahrnehmung von Oberflachenfarben, Beitrage zur Farbenpsychologie auf Grund von Untersuchungen an Fallen mit erworbenen, durch zerebrale Lasionen bedingten Farbensinnstorungen, Ztschr f Psychol **84** 193-257, 1920

13 Goldstein, K, and Gelb, A Zur Psychologie des optischen Wahrnehmungs- und Erkennungsvorgangs, Ztschr f d ges Neurol u Psychiat **41** 1-142, 1918

OBJECTIVE DEPARTURES FROM THE PERIMETRIC FIELDS OF VISION

Most of the aforementioned subjective disturbances are admittedly elusive However, they can be systematically explored by special methods of investigation, which are as objective as perimetry and tangent screen studies Some of the methods which have been employed in the past may be mentioned 1 The pointing experiment of Poppelreuter,[14] who advocated the use of a "haptic perimeter," and of Best[15] With this method the patient is required to point manually at a target presented in his field of vision[16] 2 Bisection of lines, a simple laboratory experiment adapted by Best[15] for the exploration of defective fields Here the patient is instructed to bisect a line presented in any one meridian while fixing at one end 3 Prolonged exposure of a given target in the field of vision (Poppelreuter[14], Goldstein[17]) The subject is asked to fix at a target and report the changes which may occur in the field of vision during a period of fixation 4 Double stimulation, as described by Wundt and others[18] for the cutaneous senses The patient is told to fix at a point and describe the appearance of objects exhibited simultaneously on either side of the point of fixation 5 Tachistoscopy, recommended by numerous authors since World War I (Poppelreuter[14], Fuchs[8] and Goldstein[17]) Stimuli are exposed at various speeds to the light-adapted or the dark-adapted eye, and the subject describes what he sees 6 After-imagery, as used originally by Bruckner,[19] by Fuchs[8] and, more recently, by Ruesch[20] The person is instructed to report the after-images he may see after visual stimulation under varied and specified conditions

14 Poppelreuter, W Die psychischen Schadigungen durch Kopfschuss im Kriege 1914-1916 Die Storungen der niederen und hoheren Sehleistungen durch Verletzungen des Okzipitalhirns, Leipzig, Leopold Voss, 1917, vol 1

15 Best, F Hemianopsie und Seelenblindheit bei Hirnverletzungen, Arch f Ophth **93** 97, 1917

16 Goldstein (Constriction of Visual Fields, Arch Neurol & Psychiat **50** 486-487 [Oct] 1943 Goldstein and Gelb[25]), besides stressing the importance of pointing," introduced a special "string perimeter" which allows for perimetric determinations at various distances from the patient In this way, the "tubular" (concentric) constriction of visual fields in some cases of organic disease can be demonstrated to vary with the distance of the targets from the patient

17 Goldstein, K After Effects of Brain Injuries in War, New York, Grune & Stratton, Inc, 1942

18 Wundt, W Beitrage zur Theorie der Sinneswahrnehmung, Leipzig, C F Winter, 1862, p 62 Ranschburg, P Ueber Hemmung gleichzeitiger Reizwirkungen, Ztschr f Psychol **30** 39-86, 1902

19 Bruckner, A Zur Frage der Lokalisation des Kontrastes und verwandter Erscheinungen in der Sehsinnsubstanz, Ztschr f Augenh **38** 1-14, 1917

20 Ruesch, J Dark Adaptation, Negative After-Images, Tachistoscopic Examinations and Reaction Time in Head Injuries, J Neurosurg **1** 243-251, 1944

Obviously, this list of methods is not all inclusive,[21] but these procedures have been found to be useful in exploring the various principles underlying visual functions in a defective substrate Such functions will become apparent in the form of objective depai tures from the perimetric fields of vision For example, the pointing test or the bisection of lines can reveal systematic errors in relative and absolute localization in the visual space [22] The amount and direction of errors thus elicited will indicate whether or not the median plane of the field of vision has shifted and a pseudofovea formed Such a shifting of the median plane may or may not be uncovered by perimetric examination In cases in which perimetric study fails to reveal this shift while bisection of lines and the pointing test make it manifest, one speaks of an "objective depai ture" from the perimetric field This particular departure would demonstrate the principle of functional organization of the field of vision about a center of distinctness regardless of whether or not the corresponding original anatomic substrate is present The classic observations and deductions on this topic were described during and after World War I For an excellent review of the entire subject, the reader is referred to the paper by Kluver [23]

The formation of a new fovea and the associated phenomena relate to the spatial organization of the field of vision However, there are other functions which involve both spatial and temporal factors in perceptual organization These functions can be made apparent through such methods as prolonged exposure, double and simultaneous stimulation, tachistoscopy and after-imagery

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21 Other methods are, e g, the use of visual flicker, as suggested by Kluver's ablation experiments on monkeys (Kluver, H Functional Significance of the Geniculo-Striate System, Biol Symposia **7** 253-299, 1942) and applied by Riddell (Use of the Flicker Phenomenon in the Investigation of the Field of Vision, Brit J Ophth **20** 385-410, 1936) to the exploration of visual fields, and the use of the stroboscope (Werner, H, and Thuma, B D A Deficiency in the Perception of Apparent Motion in Children with Brain Injury, Am J Psychol **55** 58-67, 1942)

22 It should be borne in mind that the kinesthetic sense and the motor functions of the extremity used in pointing or bisecting must be intact

23 Kluver, H Visual Disturbances After Cerebral Lesions, Psychol Bull **24** 316-358, 1927 Kluver succinctly stated the conclusions from observations on patients with injuries of the brain in World War I to this effect Studies on anatomic localization became barren in spite of the wealth of material once the general topography of the "cortical retina" had been established By contrast, research on higher perceptual functions revealed that these functions were relatively independent of specific structures For these reasons, Klüver joined such authors as Goldstein and Gelb (footnotes 13 and 17) in stressing the need for continuing both "phenomenologic" and experimental exploration of these perceptive processes in defective visual fields

FUNCTIONS INVOLVING TEMPORAL AND SPATIAL FACTORS

The phenomena which we wish to consider in particular are (*a*) fluctuation, (*b*) extinction and (*c*) completion of images By fluctuation we mean that the visual image in the affected region may fluctuate in distinctness at a varying rate or may disappear and reappear at a certain rate By extinction we mean that during fixation at a given point the image disappears completely in any part of the field of vision after a certain period Between extinction and fluctuation of the visual image a continuum of intermediate states may be found These gradations may be subsumed under the term "obscuration" (dimming) of the image In certain cases extinction can be demonstrated only under special conditions Objects exposed in impaired parts of the field may become invisible on simultaneous exhibition of another stimulus in a less impaired or in an intact part [24] Completion of images should be understood as follows Images involving both impaired and comparatively unimpaired regions of a field of vision are "completed" under certain conditions This takes place in spite of the fact that the image is invisible if presented to the impaired region alone Again, several gradations are possible Sometimes only partial continuation of figures into the defective region is encountered Total completion has been reported to occur specifically (*a*) if the test figures possess good contour and are symmetric, simple configurations and (*b*) if the figures are not too large and one half or more of their area is exposed to the intact portion of the field of vision

Of these three phenomena, fluctuation is the most common As a rule, extinction can be found to occur in regions otherwise characterized by some degree of fluctuation Completion seemingly stands by itself, unrelated to fluctuation and extinction A review of the literature reveals, indeed, that although both the phenomena of extinction and that of completion have been known since World War I their functional relationship has not been considered

HISTORICAL REVIEW

The effect of completion was apparently discovered by Poppelreuter [14] and later confirmed in many experiments by Fuchs [8] and by

24 Halstead's (Function of the Frontal Lobe in Man The Dynamic Visual Field, Arch Neurol & Psychiat **49** 633 [April] 1943) concept of the dynamic field is actually based on a special form of extinction elicited by "double stimulation" He defines as "dynamic field" that portion of the total visual field in which a target is seen peripherally while a form discrimination is being made (simultaneously) in the center of the field

Goldstein and Gelb [25] These authors agree on the following facts Whenever simple figures (solid and outline circles, solid squares) are exposed to hemianoptic subjects in such a wey that one half or more of the figure falls into the intact portion and the remainder into the defective portion of the visual field, the figure is seen completely, on the other hand, asymmetric and more complex configurations (letters, drawings) may be recognized by the patient but are never completed There is unanimity in these observations, but their original interpretation by Poppelreuter has been contested by Fuchs [8] and, again, by Goldstein and Gelb [25] Poppelreuter [14] himself assumed that the effect of completion was produced by a "totalizing Gestalt conception" (*totalisierende Gestaltauffassung*) But he explained the latter as a psychologic process which provides a simple filling in of missing parts in familiar figures Thus, he did not consider the possibility of an immediate perceptual process in the visual cortex itself which might account for the actual completion of the image In a series of experiments, Fuchs [8] was able to show that it is indeed not familiarity with, but the simplicity of, the configuration that is conducive to the completion effect In this way, he put the effect on a basis similar to that for phenomena observed for the physiologic blindspot [26] and for after-images in subjects with intact visual fields

After-images have frequently been shown to exhibit such Gestalt effects as "simplification" and "good continuation" [27] But in spite of the theoretic difference between Poppelreuter and the representatives of the Gestalt school, all these authors have stressed that objectively incomplete configurations are just as readily "completed" in defective regions as though they were actually complete Their observations, therefore, give only incidental evidence for a functional connection between injured and intact areas [28]

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25 Goldstein, K, and Gelb, A Psychologische Analysen hirnpathologischer Fälle auf Grund von Untersuchungen Hirnverletzter, Leipzig, Johann Ambrosius Barth, 1920

26 In an old experiment described by Volkmann (1853) and by Wittich (1863) a cross is exposed in such a way that its center falls on the physiologic blindspot [42] Under such conditions the cross is seen as complete, even though the central portion may actually be omitted from the test figure

27 Rothschild, N Ueber den Einfluss der Gestalt auf das negative Nachbild ruhender visueller Figuren, Arch f Ophth **112** 1-28, 1923

28 In point of fact, in 1 of the cases of Gelb and Goldstein [10] such an interaction was shown between the two halves of a single visual field On tachistoscopic examination this patient, who was hemiamblyopic, was found to have micropsia in the injured half of his field, objects in the intact half retained their normal size However, if an object was presented in such a way that portions of it fell to

(Footnote continued on next page)

Such dynamic interaction is more apparent in the phenomenon of extinction (Bender and Furlow [29]), which, in contrast to the completion effect, tends to make the "actual," or "functioning," field of vision much smaller than the fields which would be inferred to exist from perimetric examination alone The phenomenon was known to Oppenheim,[30] who described it in his textbook of neurology in 1900 and 1923 Head [31] reported it in a case of right hemianopsia He found that if his patient had both eyes open and "two similar objects were exposed at exactly the same distance from the fixation point, that to the right was frequently not appreciated, although it might be recognized if shown alone"

Poppelreuter [14] attempted to explain the effect as a result of a hemianoptic "weakness of attention" He claimed that an "active direction of attention toward the impaired part of the field" would make simultaneous perception in both half-fields possible Goldstein, however, has stressed consistently [32] that such an undefined psychologic concept as "attention" cannot be invoked to explain these phenomena He assumed that they give evidence of a general physiologic principle, which he termed "equalization" This equalization is an expression of the continuous background activity in the central nervous system It tends to abolish existing excitation processes by raising the local threshold after each process It thereby insures temporal and spatial segregation of these processes from each other Over partly impaired cortex this equalization takes place in an irregular fashion, it usually enhances the intact portions and depresses the impaired portions on simultaneous excitation

More recently, this dynamic interaction between the impaired and the unimpaired part of a field of vision was demonstrated in a patient with a gunshot wound involving the left parieto-occipital lobe [29] Since then, a considerable number of patients with trauma of the central nervous system have been found to exhibit the phenomenon in the

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either side of the dividing line between the halves of the field, the whole object was reduced in size, in proportion to the extent to which the object overlapped into the impaired area

29 Bender, M B, and Furlow, L T Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch Neurol & Psychiat **53** 29-33 (Jan) 1945

30 Oppenheim, H Diseases of the Nervous System, translated by E E Mayer, Philadelphia, J B Lippincott & Co, 1900, p 59, Lehrbuch der Nervenkrankheiten, ed 7, Berlin, S Karger, 1923, p 113

31 Head, H Aphasia and Kindred Disorders of Speech, London, Cambridge University Press, 1926, vol 1, p 439, vol 2, p 108

32 Goldstein, K, in discussion on Bender, M B, and Furlow, L T Phenomenon of Visual Extinction in Homonymous Fields, Tr Am Neurol A **70** 87-92, 1944, footnote 17

visual sphere, and frequently for other modalities, especially the cutaneous senses,[33] the nature of the phenomenon depending of course on the site of the lesion The name "extinction" was given to the clinical phenomenon, in analogy to Dusser de Barenne's[34] physiologic term Reider[35] recently examined a similar group of patients and called the condition the "suppression" phenomenon

Although pathologic fluctuation, extinction and completion were thus discovered and rediscovered in a somewhat haphazard manner, it is well to remember that equivalents or analogies for each of these phenomena in the perceptions of normal subjects were already known to experimental psychologists and had been analyzed in systematic laboratory research Thus, fluctuation in defective fields is actually only a special case of the so-called fluctuation of attention, which the aurist Urbantschitsch[36] discovered as early as 1875 to be a general phenomenon for weak auditory stimuli in every observer Guilford[37] (1926), in his reevaluation of previous research, described vividly how this problem of fluctuation of attention has been "settled and unsettled at least four times in as many generations of experimental psychology" Explanations in terms of peripheral and of central factors have been proposed More recently, intermodal aspects of fluctuation in normal persons have come to the fore By emphasis on the latter, Guilford himself could establish a definite central factor in the causation of these phenomena But even the more recent experiments of Fry and Robertson[38] left the problem essentially unsettled

Effects akin to extinction with double stimulation in defective fields have been adduced in theories about the deviations of normal binocular fields of vision from the geometric horopter (the sum of those spatial points whose images at a given ocular position fall onto corresponding retinal points) Thus, the Aubert-Forster phenomenon,[39]

33 Bender, M B Extinction and Precipitation of Cutaneous Sensations, Arch Neurol & Psychiat **54** 1-9 (July) 1945

34 Dusser de Barenne, G, and McCulloch, W S Factors for Facilitation and Extinction in the Central Nervous System, J Neurophysiol **2**·319-355, 1939

35 Reider, N Phenomena of Sensory Suppression, Arch Neurol & Psychiat this issue, p 583

36 Urbantschitsch, V Ueber eine Eigentumlichkeit der Schallempfindungen geringster Intensitat, Centralbl f d med Wissensch **13**.625-628, 1875

37 Guilford, F P Fluctuations of Attention with Weak Visual Stimuli, Am J Psychol **38**.534-585, 1926

38 Fry, G A, and Robertson, V M The Physiological Basis of the Periodic Merging of Area into Background, Am J Psychol **47**·644-655, 1935

39 (*a*) Aubert, H Physiologie der Netzhaut, Breslau, E Morgenstern, 1865, pp 234-253 (*b*) Jaensch, E R Zur Analyse der Gesichtswahrnehmungen, Ztschr f Psychol (supp) **4**·1-26, 1909 (*c*) Freeman, E Anomalies of Visual Acuity

(*Footnote continued on next page*)

i e, the shrinking of the normal visual field with increase in perceived distance, has been combined with observations on the intensification of colors in micropsia induced with a plus lens (Koster phenomenon) in Kaila's [39d] hypothesis of a "central inhibition of images" (*Hemmung*) This inhibition is presumed to produce qualitative and quantitative changes in perception as soon as the observer assumes a set for "distance" From a more physiologic point of view, Fry [40] investigated the suppression of a single flash of light immediately followed by a second flash of light projected onto adjacent areas of the retina Like Pieron,[41] Fry stressed peripheral factors in his attempts to explain these phenomena

Completion, finally, has received even more attention from the experimental psychologists than has fluctuation or extinction For in the normal subject the completion effect is represented by the phenomenon of "continuation" and of "closure" of visual configurations, as studied by the Gestalt school Closure of incomplete Gestalten was found to occur particularly under conditions of rapid tachistoscopic exposure or low illumination, in other words, under conditions approaching the instability of a pathologic visual field [42]

In the present study, the phenomena of completion and extinction were investigated in detail in a series of patients with damage to the brain and some of the determining factors, particularly the time relationships involved, analyzed Observations made on after-images and in tachistoscopic and perimetric examinations were compared for each patient Various supplementary methods as previously listed were applied whenever it seemed indicated The following questions were considered with regard to the processes in their visual fields

1 Is extinction an important factor in the visual performance of unselected groups of patients with partial field defects?

2 Do phenomena of "extinction" and "completion" occur with about equal frequency, and, if so, are they likely to be related?

3 Is it thus possible to consider extinction and completion in conjunction with each other and thereby to understand more clearly the dynamics of impaired (and unimpaired) visual fields?

4 In particular, is it feasible to explain thus some of the incongruities in fields obtained with the methods of perimetry, tachistoscopy and after-imagery?

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40 Fry, G A Depression of Activity Aroused by a Flash of Light by Applying a Second Flash Immediately Afterwards to Adjacent Areas of Retina, Am J Physiol **108** 701-707, 1934

41 Pieron, H Le processus du metacontraste, J de psychol norm et path **31** 5-24, 1935

42 Koffka, K Principles of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc, 1935, p 145

CASE MATERIAL

Three cases from a larger group[43] were selected to illustrate these relationships

CASE 1.—A 26 year old Marine, was injured in action by shrapnel and a hand grenade. He suffered multiple wounds of the head and body. Aboard a hospital ship, it was noted that he had paralysis of the left arm and leg. There was no aphasia, even though the patient had always been left handed. There was a depressed fracture of the right temporal bone, with a metallic fragment deeply embedded in the brain (fig. 1). His vision was "foggy," and four weeks after the injury a left homonymous hemianopsia was recognized in confrontation tests. When received at the hospital with which we were associated, he still showed a left hemisensory syndrome, and repeated perimetric and tangent screen examinations revealed a macula-splitting left homonymous hemianopsia (fig. 2). At this time, fourteen weeks after the injury, the patient was no longer aware of his field defect, and objects did not appear to be split on fixation, as they had during the first two months following his injury, when he saw only the right half of each object.

Tests for Completion Phenomenon.—After-Imagery. The patient was confronted with an American flag, measuring 10 by 18 cm., drawn in complementary colors, and he was asked to focus his gaze on the star in the right lower corner, 30 cm. away from him. He was also instructed to find this star by looking for it from right to left. It was found that during fixation the patient did not perceive anything to the left of his fixation point (fig. 3*A*). A pencil which was moved back and forth over the flag immediately to the left of the point of fixation was not

43 The present report confines itself to observations on and deductions made from cases of presumably pure "organic" disease. In addition to these cases, our series included several in which perceptual disturbances had been classified by us as hysterical or psychotic. Nevertheless, these were studied by the same methods for comparative purposes. We realize that the distinction between the so-called organic and the nonorganic disturbances is usually arbitrary. But we used the following main criteria in accepting the changes in perception as being directly related to structural defects: (1) presence of a demonstrable lesion in the brain, (2) history of subjective disturbances consequent to the cerebral injury and related to the perceptual changes studied, (3) consistency of the patient's reports during different examinations and under varied conditions, (4) conformity of the subjective and objective changes observed to psychologic, pertinent, well established principles of normal function, as well as to facts already known about pathologic changes in perception following cerebral lesions, and (5) similarity of a patient's special symptoms to those shown by the majority of the patients in the group suspected of having an organic lesion. This consistency among patients was so striking that we could use it as one of the principal criteria. With these standards the differentiation could be made without too much difficulty. However, the perceptual disturbances in the whole series formed a continuum from an "organic" to a "psychogenic" syndrome. For that reason, it is expected that continued controlled experiments on perception in subjects with organic lesions will lead eventually to a fuller understanding of the pathologic processes in patients whose disorders have still to be considered as "merely neurotic."

seen, even though this moving stimulus was applied for the entire thirty second period of focusing In the after-image, however, the patient saw a considerable portion of the left half of the field, as indicated by the sketch (fig 3 *B*) This increase in the area of visibility represents a type of completion The extent of "completion" to the left (beyond the fixation point) amounted to from 5 to 9 degrees The phenomenon was consistent from trial to trial and from day to day

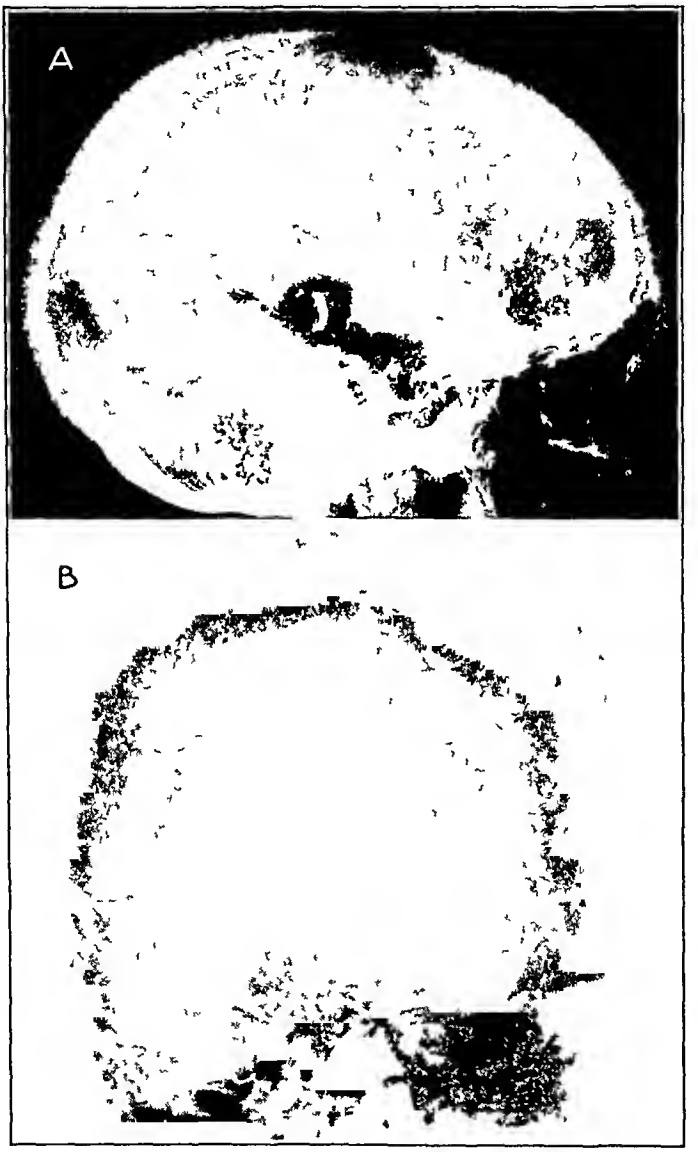

Fig 1 (case 1) —Roentgenograms of the skull, right lateral (*A*) and anteroposterior (*B*) views On Aug 2, 1945 (ten months after the injury) the largest metallic fragment was surgically removed from the lower anterior portion of the thalamus The state of the fields and the dynamic aspects of the patient's visual organization were unchanged after this operation

Tachistoscopic Exposure The patient was seated in a totally darkened room, at a distance of 75 cm from a milk glass screen, 36 by 44 cm in size Behind the screen, and shielded from the patient's view, was a tachistoscope In the center

of the screen was a small black disk, 0 5 cm in diameter, which served as a point of fixation during the experiments to be described To insure maintained fixation on this point in the center of the screen, the whole screen was faintly illuminated (0 07 foot candle) from the side opposite the patient [44] By means of a small cone of light, moving behind the screen, the patient's fields were plotted (as though on a tangent screen), and the existence of the complete homonymous hemianopsia was found to be confirmed under these conditions

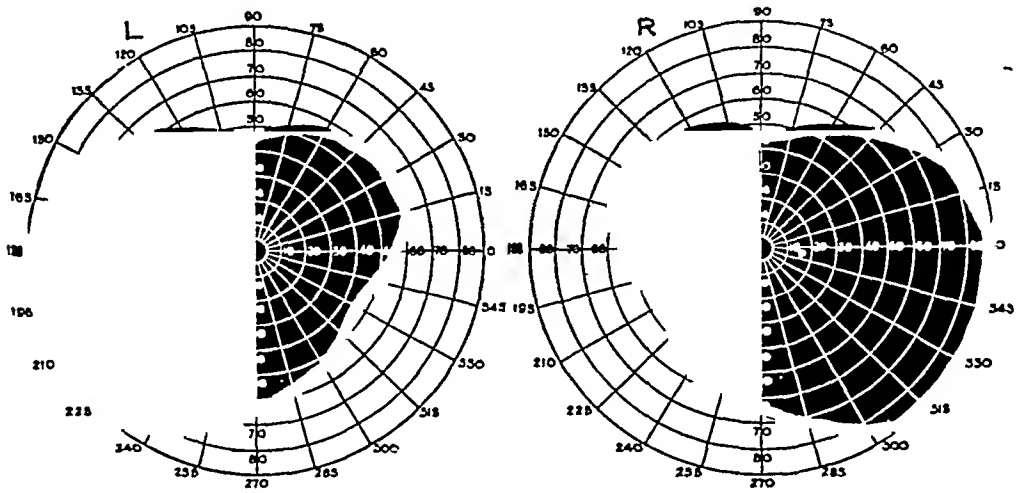

Fig 2 (case 1) —Left homonymous hemianopsia The "macula splitting," as well as complete amaurosis in the left half of each field, were constant changes found in all perimetric examinations

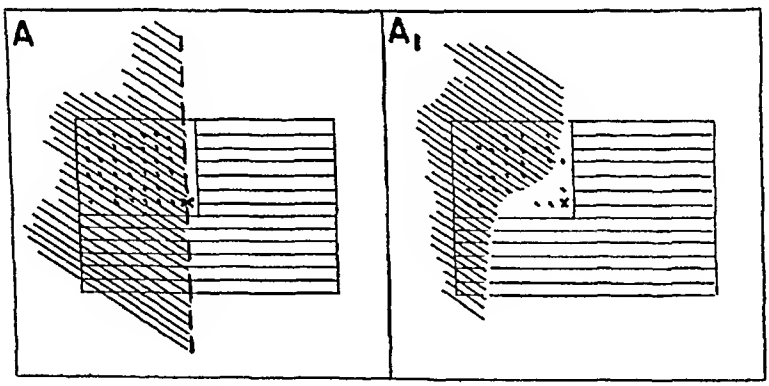

Fig 3 (case 1) —*A*, appearance of drawing of the American flag (10 by 18 cm) during maintained fixation on a star in the right lower corner, indicated by *X*, 30 cm from patient's eyes The shaded area indicates the region of apparent blindness The macula appeared to be "split" A_1, appearance of the complementary after-image of the drawing, after a 30 second period of exposure A considerable portion of the flag to the left of the fixation point had become visible in the negative after-image, representing a form of "completion"

44 This was done in each instance after a period of five minutes of total darkness had been allowed for dark adaptation The amount of adaptation achieved by the patient prior to entering the examining room was not controlled For this reason there was no strict uniformity of initial adaptation from test session to test session and from patient to patient, but the differences were probably negligible and became of still less significance during the latter part of each session

A pattern of four dots, arranged as an oblong (fig 4 *A*) was projected against the screen (time exposure) The pairs of dots were 14 cm to the right and to the left of the fixation point, a distance which corresponded under the experimental conditions to an angular distance of about 10 degrees With continuous exposure, our patient saw only the two dots to the right, that is, in his uninvolved half fields, regardless of whether both eyes, the right eye or the left eye was used

Experiment 1 Tachistoscopic exposure of this pattern of dots (fig 4 *A*) at all speeds from 1 to 1/150 second did not increase the area seen by the patient He never reported more than the two dots situated in his right field of vision, the two dots in his left field were not seen under these conditions A brief negative

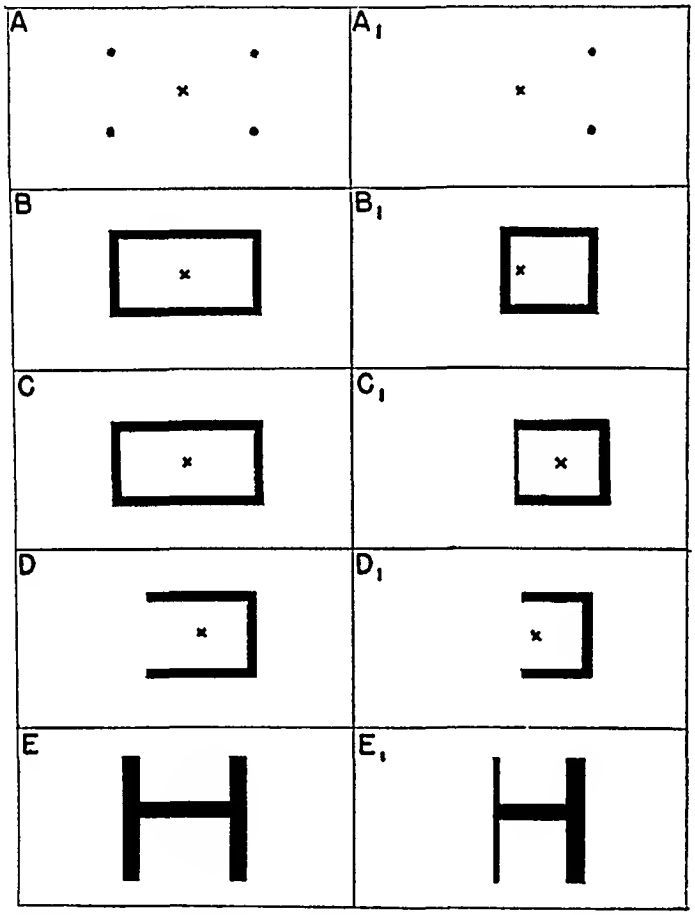

Fig 4 (case 1)—Test patterns used in investigating completion effects on tachistoscopic exposure (*A-D*) All presented figures (with the exception of *C*) subtended an angle of 10 degrees to either side of the fixation point (*X*) What the patient saw on rapid exposure (1/150 and 1/100 second) is indicated in the corresponding figures A_1-D_1

after-image of the perceived dots was seen with exposures of 1/100 and 1/150 second but not with lower speeds

Experiment 2 An oblong (fig 4 *B*) with vertical edges, again 14 cm, or 10 degrees, to either side of the fixation point, was substituted for the four dot pattern At a speed of 1/150 second the patient saw this pattern as a square (fig 4 B_1) He was definite in stating that it was a complete and undistorted square Occasionally, however, on repeated testing with speeds of 1/100 to 1/150 second, he

volunteered that the left vertical side of the square appeared thinner than the other three lines (fig 4 C_1) The same square was seen as incomplete about half the time with speeds below 1/50 second, and it appeared always incomplete with speeds below 1/20 second

Experiment 3 An "incomplete square" (fig 4 *D*) was substituted for the oblong The figure opened to the patient's left When this incomplete square was flashed at a speed of 1/150 second, the patient felt that this was "not as good a square" and asked the experimenter whether it was actually complete He was not certain whether he saw it as incomplete On rapid testing with complete and incomplete figures alternating at random, he always said that the two figures were different He was positive that the presented complete oblong, such as that in figure 4 *B* and *C*, was a complete square, but he was hesitant in saying what the exposed incomplete square such as that in figure 4 *D*, looked like He stated characteristically, "I just can't tell because I don't see all of it"

Experiment 4 A letter *H* in heavy black lines, with the verticals again about 10 degrees to either side of the fixation point (fig 4 *E*), was exposed at a speed of 1/150 second The patient saw a complete *H*, but the vertical line to his left appeared thinner than the one to his right (fig 4 E_1)

In order to maintain proper fixation, various precautions were taken throughout the tachistoscopic tests Immediately preceding each exposure the patient was instructed to check on his fixation and to report whether he was ready [45] Furthermore, the exposures of complete and incomplete oblongs were interspersed with exposures of the four dot pattern The patient always reported only the two dots to his right, regardless of the speed at which they were presented, thus indicating that his fixation did not shift to any great extent

Comment—According to his visual after-imagery, the patient was not as hemianoptic as was suspected from the perimetric studies There was a tendency to complete the image It will be noted that the "completion" of the image never occurred during prolonged fixation, in which movements of the eyes must have repeatedly carried parts of the left half of the flag over the fixation point and into the patient's right, or better, field Yet, in the after-image the flag appeared with considerable portions added to the left In other words, the patient's hemianopsia was macula splitting during exposure, but in the after-image the macula seemed to be spared The phenomenon cannot be explained in terms of the usual behavior of after-images which is demonstrable in normal subjects There, one finds frequently the characteristic simplification of the configuration which has been

45 In these circumstances, it was frequently noted on replotting the central field that the line of division between the scotomatous area and the area of full vision had shifted to the left by about 5 cm This shift of the midline by 3 to 4 degrees can be taken as an indication that the patient was now using a pseudofovea for fixation, since he felt that he was still maintaining fixation on the disk in the center It is not impossible that such an unnoticed shift of the patient's eyes to his left might have occurred in some of the test exposures But the extent of the shift (3 degrees) is not sufficient to explain the patient's sudden ability (under rapid exposure) to see objects at an angular distance of 10 degrees from his original fixation point

exposed, for instance, rounding of protruding corners, loss of inside detail and occasionally, a "filling in" of gaps in surface or contour [42] Yet in our case the portion that appeared to be "filled in" in the after-image did not produce a smoothing of contours, on the contrary, it represented a fairly irregular addition, which can be interpreted only in terms of a reduction in the size of the scotoma under conditions of after-imagery

On tachistoscopic tests this patient undoubtedly showed completion of a continuous figure into the scotomatous area whenever the speed of exposure was sufficiently rapid The figures were seen as incomplete with lower speeds Whenever the patient did complete a figure, part of which fell on the scotomatous region of his field, it was not in the sense of a "psychologic filling in" of a missing part (as suggested by Poppelreuter [14]) Completion did not occur when the presented figure was actually incomplete The latter observation would seem to conflict with those made under similar conditions by the Gestalt school, according to which completion appeared to be a form of "Gestalt closure"

As previously noted, both Poppelreuter [14] and Fuchs [8] found that those parts of the stimulus pattern which fell into amaurotic or amblyopic regions might be omitted without interfering with the completion effect Fuchs, however, pointed out that this was a matter of degree, the effect was dependent on the proportion between the part of the figure exposed to the intact region of the field and the part exposed to the impaired region These spatial factors were emphasized by Fuchs, while he gave only scanty attention to the temporal factors which we have stressed in the present study

However, a Gestalt factor in a slightly different sense, viz, "continuation," must have been operative in producing the completion effect in our patient If a configuration was discontinuous in all quadrants, completion did not take place [46]

CASE 2.—A 20 year old seaman first class exhibited visual field defects after he had sustained injuries to the head and face in action in the Pacific A bullet had entered the cranial cavity through the right posterior parietal region and lodged in the right frontal lobe (fig 5) When he came under our observation, nine months after the injury, he showed a mild left hemiparesis and a characteristic hemisensory syndrome Perimetric examination of the visual fields showed a defect in the extreme periphery of the lower left temporal quadrant On prolonged fixation at a central point, he exhibited continual fluctuation and obscuration in the left half-fields, particularly in the lower left quadrants (fig 6)

46 Thus, he could see only one half of a dot pattern, i e, he saw it in keeping with his perimetric field and in contrast to the oblong, which was completed Additional experiments showed that this effect was due to discontinuity of the pattern and not to the fact that the four dots, in combination, covered less area than the oblong

Extinction with Double Stimulation Method—However, when this patient's fields were plotted against a dimly illuminated screen (0 07 foot candle), neither the movement of a cone of light 5 cm in diameter nor the shadow of a hand was perceived by him at any angular distance exceeding 11 degrees from the fixation point, in the lower left quadrant In other words, the illuminated surface, surrounded by a dark background and extending to either side of the fixation point, was conducive to continual "extinction" in the defective field This extinction could be shown to occur in this patient on double stimulation in the heteronymous

Fig 5 (case 2)—Roentgenogram of the skull, right lateral view The bullet penetrated the right parietal bone and came to rest in the right frontal area Note the defect and fragments of bone in the parietal region

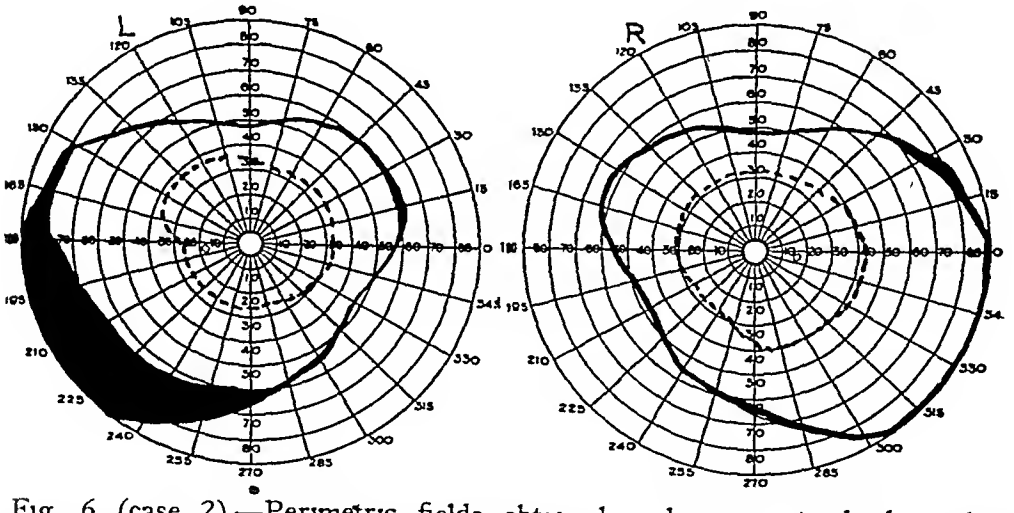

Fig 6 (case 2)—Perimetric fields obtained under our standard conditions (illumination, 7½ foot candles, distance, 33 cm , 1 degree targets) nine months after the head injury The black areas indicate no perception for motion, the lines of dashes, outline of fields for red The defect in the extreme periphery of the lower left temporal quadrant suggested an earlier incomplete homonymous hemianopsia On prolonged fixation, there were rapid and continual fluctuation and obscuration in the temporal half of the left field of vision, particularly in the lower quadrants On double stimulation to the right and the left of the median plane, everything in the left lower quadrants became extinct at and beyond 11 degrees from the fixation point

half-fields He exhibited the same sort of extinction for simultaneous stimulation of the skin receptors on the contralateral side of his body

However, there was no evidence of spatial disorientation in the affected half-fields, a condition which may have been due to the fact that the density of the "dynamic" scotoma increased steadily toward the periphery and finally merged into the peripheral absolute scotoma There were, furthermore, no indications of increased ocular unrest, nor was there any awareness of the scotoma

After-Imagery—The patient's after-images, in contrast to those in our first case, did not illustrate the principle under consideration, since he saw the full image of the original flag during exposure In the after-image, however, the field defect was represented by a lack of chroma on the left side of the image, an observation which suggests an interference of the opposite half-fields Thus, he saw the flag exposed in his left field of vision as gray in the after-image With repeated testing, the after-image assumed a faint color, showing a light blue field and pink stripes

Completion Phenomenon on Tachistoscopic Exposure—Under the same experimental conditions as those in case 1, the patient was seated in a darkened room 40 cm from the opaque screen of the tachistoscope, and the field defect was plotted on the screen as it extended toward the periphery in the patient's left lower quadrant, at 8 cm (11 degrees) from the fixation point In the area of the scotoma not even movement of a hand was appreciated beyond this angular distance

The four dot pattern was given with time exposure and then at varying speeds Only three dots were seen, with the dot in the lower left corner always missing, when the time exposure was greater than 1 second

The oblong was then exposed at 1/150 second, and appeared as a complete and undistorted figure This effect was always obtained with 1/150 second's exposure Conversely, the oblong was always seen as incomplete in the lower left quadrant with a 1 second exposure In 7 out of 10 exposures it was incomplete with ½ second's exposure and in 4 out of 10 exposures, with 1/10 second's exposure, with 1/150 second's exposure it was complete 7 out of 10 times

Comment—This case suggested that the completion in tachistoscopic exposure was nearly a direct function of the speed of exposure The higher the speed, the more readily was the configuration completed Control exposures of presented incomplete figures again showed that normal "closure" of patterns could not be the primary factor Since the scotoma, in contrast to the conditions in our first case, was only relative in the regions close to the macula the completion effect appeared more clearly as a function of "suppressed" extinction That is higher speeds of exposure made extinction (which is presumed to take time) impossible, while continuous exposure with moderate brightness, or simultaneous stimulations, resulted in extinction in the defective area

Occasionally, the patient reported negative after-images after a tachistoscopic exposure The images were too faint and too few to be analyzed Otherwise we should have tried to determine whether these negative after-images showed the same amount of completion

as the immediately preceding original images or whether they exceeded the latter by being even more "complete" However, the occurrence of after-images as such suggested the hypothesis that completion on tachistoscopic exposure may be merely a result of the appearance of negative after-images The completion of the latter would be the primary phenomenon, and the patient, while seemingly responding to the original images, would actually be describing the appearance of the after-effect

After-images are indeed unavoidable during tachistoscopic examinations unless special precautions are taken to prevent their appearance (e g, very bright after-fields) These after-images, it has been pointed out frequently,[20] may increase the actual time of exposure in an uncontrolled fashion If they had occurred more often in our second case, even the observed increase in completion with increasing speed of exposure could be interpreted in terms of steady after-image completion Throughout our series of cases, we noted that very rapid tachistoscopic exposures of configurations with strong contrast tended to produce stronger and more persistent after-images than exposures at low speed

In subsequent experiments, we therefore instructed our patients always to report whether an after-image (positive or negative) was seen after tachistoscopic exposure Moreover, bright after-fields were frequently given immediately after tachistoscopic exposure in order to abolish after-images which might have been formed Our third case illustrates the results with these after-fields and with additional controls, in the conditions of stimulation

CASE 3—Our third example was provided by a patient with homonymous scotomas in all four quadrants Three and a half months before he came under our observation, a 20 year old fireman first class, had been struck by shrapnel in the occiput and sustained a compound fracture of the skull (fig 7) Both occipital lobes were damaged, and there was complete blindness which lasted ten minutes For about a week he had slight aphasia and numbness in the tips of the fingers of his right hand On examination at this hospital, he complained of sensations of "electric shock" This sensation could be elicited on bending his neck All other sensory disturbances had become minimal

Examination of the oculomotor system, including vestibular reactions, revealed nothing abnormal except for spontaneous zigzag ocular movements in the horizontal plane during prolonged fixation These sudden and jerky excursions were fleeting, disappearing after one or two seconds They were particularly evident during perimetric measurements and other studies of the visual fields

The remaining outstanding symptoms were in the visual sphere Here the patient showed a condition almost complementary to that in case 2 On perimetric examination (fig 8 *A* and *B*) a large absolute scotoma was found extending 25 degrees from the fixation point in the right lower homonymous quadrants Beyond this area the scotoma extended toward the periphery, but it had much less density In the latter region the patient showed fluctuation in his ability to see even motion That is, movement was appreciated in this region but not consistently

He would suddenly find he could perceive a moving object or a light (in a dark room) in the right lower quadrant of his field of vision, but more frequently he noted that he was totally blind in this area In other words, the interval of blindness was much longer than the phase of his ability to see in this area of fluctuating function [47] Whenever he did see in this defective quadrant, he exhibited

Fig 7 (case 3)—Roentgenograms of the skull, showing large circular defect in the occiput Although the bony defect is to the left of the midline, the available evidence indicates damage to both occipital lobes

a complete spatial disorientation both in the coronal and in the sagittal plane The disorientation involved localization of points and appreciation of direction of movement [48]

47 Ordinarily, in an area of fluctuating vision (as originally defined) the phase of ability to see is longer than the interval of disappearance of the image

48 It may be assumed that both the spatial disorientation and the ocular zigzag movement, previously noted, were dependent on the fact that his scotoma did not extend with equal density all the way into the periphery The patient in our

Awareness—1 Another feature of the patient's disorganization in perception was awareness of an inequality of his subjective fields of vision He complained that his right eye was partly covered with a large circular spot of fog When he tested each eye separately, he said that the left eye was also partly covered with a cloud but that the latter seemed much smaller than the one on the right Both these subjective obstructions were localized by him to the right lower quadrant He was able to see these clouds with the eyes open or closed and they were so

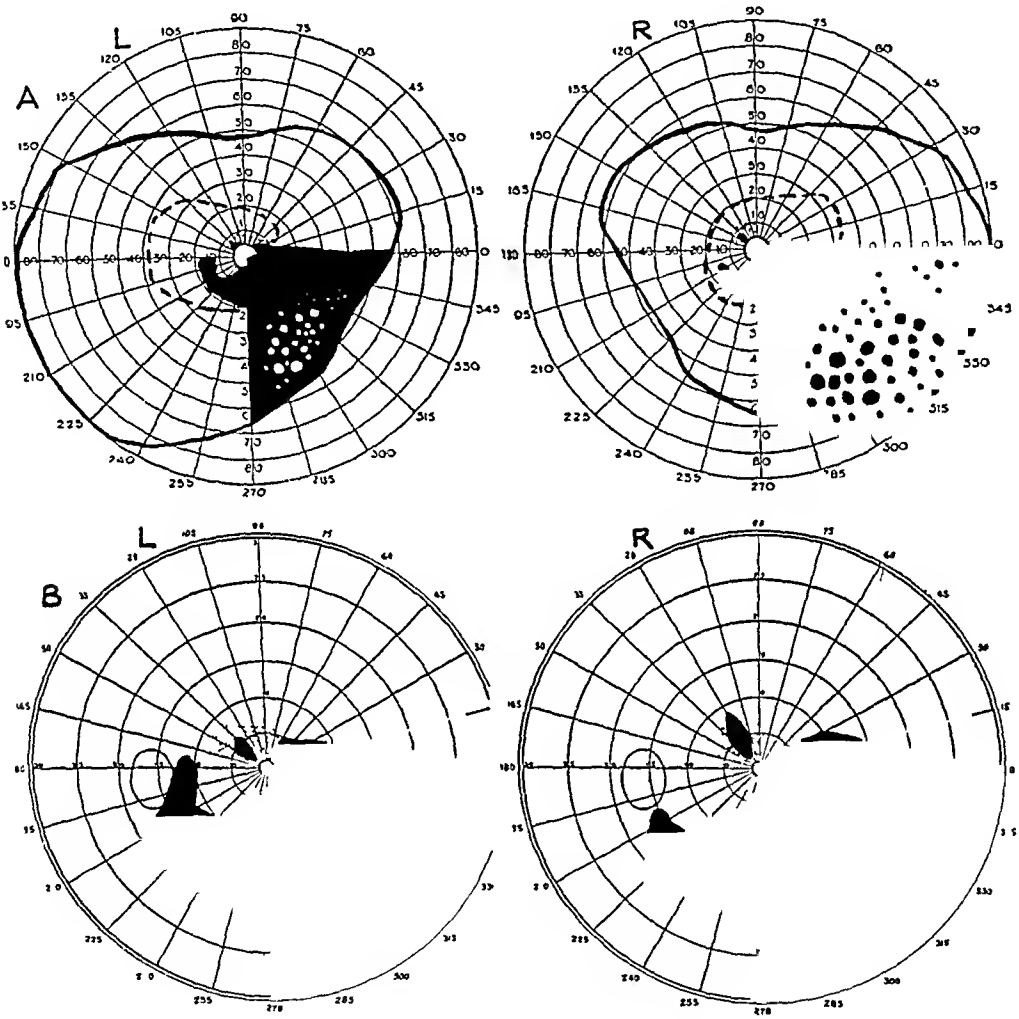

Fig 8 (case 3)—Visual fields in perimetric (*A*) and tangent screen (*B*) examinations, revealing homonymous scotomas in all four quadrants The solid black indicates zones of amaurosis, and stippling indicates amblyopia As apparent in the right inferior quadrants, the scotoma is absolute (for 1 degree targets) to 25 degrees from the fixation point Beyond that, the white stippling indicates an area in which vision was found to fluctuate At a given point, a perceived image would disappear and reappear at a variable rate, the duration of visibility was much shorter than that of invisibility In this area, the patient showed spatial disorientation and dysmorphopsia To a lesser extent he showed such disturbances in the other quadrants

pronounced that he could easily draw them (fig 9) When they were compared with the scotoma obtained on the perimeter for the right lower quadrants, the

second case in which conditions in the field were reversed, showed no awareness of scotoma, disorientation or apparent increase in spontaneous ocular movement

clouds seemed to be roughly related to the plotted defect However, they differed from the perimetric field inasmuch as the subjective scotoma appeared larger to the right eye than it appeared to the left

2 After numerous examinations over a period of weeks, the patient suddenly became aware of a "new spot of fogginess" in the upper temporal quadrant of the left eye He was not aware of a similarly situated spot in the right eye unless he tested himself repeatedly This new spot was apparently determined by the congruent scotomas as recorded in both left upper quadrants But in spite of the appearance of a "new spot" in the left eye the patient still maintained that the "right eye is worse than the left"

3 As the examinations of his visual performance were continued, he became aware of a third "spot" It was localized in the upper temporal quadrant of the right eye and was described as being yellow, like a small light This was visible to him with the eyes closed or open, but it was extremely transient Of all the spots of which he became aware, the one in the right lower quadrant was the most prominent

Bisection of Lines—With the changes in awareness of his field of vision his ability to bisect lines was altered Before he became aware of the spot in the left upper quadrant, he usually bisected the line by displacing the estimated center toward the point of fixation The degree of displacement was the same for both eyes Afterward, the displacement was in the same direction but the degree became most pronounced in the temporal half of the left eye

Fig 9 (case 3)—Patient's drawing of the scotomas, of which he was constantly aware Although the plotted scotomas are more or less congruent, the patient felt that his right eye was "worse" than his left, because a large fog seemed to cover it from the right On testing himself, he found a considerably smaller "fog" in the left eye In his drawings the patient spontaneously indicated the boundaries of his visual fields by adding the crude outline of an eye

Completion on After-Imagery—During exposure of the American flag, drawn in complementary colors, at a distance of 30 cm the patient did not see the whole pattern when tested under any condition provided fixation was maintained at a given point The portions in the pattern which seemed to him to be missing during prolonged fixation corresponded to the subjective field with its awareness of scotoma

1 Fixation with Both Eyes (*a*) The flag in his entire lower right field was invisible to him The region of invisibility extended into his visual field "like a bulge" (fig 10 *A*)

(*b*) In the after-image, however, after 60 seconds' exposure, somewhat less was "cut off" from the original image (fig 10 A_1)

2 *Fixation Only with His Right Eye* (*a*) During fixation the patient reported that there was an area of obscured vision (to the right of the point of fixation) This area appeared smaller than the one reported on fixation with both eyes (fig 10 *B*) In addition to the area of obscured vision to the right, the patient reported an area of complete haziness above and to the left of the fixation point This represented evidently the insular scotoma in the upper left quadrant (cf patient's visual fields, figure 8)

(*b*) In the after-image, the scotoma in the upper nasal quadrant was not manifest Moreover, the defect in the lower temporal quadrant had become much smaller (fig 10 B_1) The completion effect elicited by stimulation of the right eye was evidently more pronounced than that obtained with stimulation of both eyes

3 (*a*) *Fixation with His Left Eye* The defect in the lower right quadrant was at a sharper angle and less extensive than the obscured area noted on fixing with the right eye (cf patient's attempt to draw his own visual fields, figure 9) The patient again noted an obscure area in the upper left quadrant (fig 10 *C*)

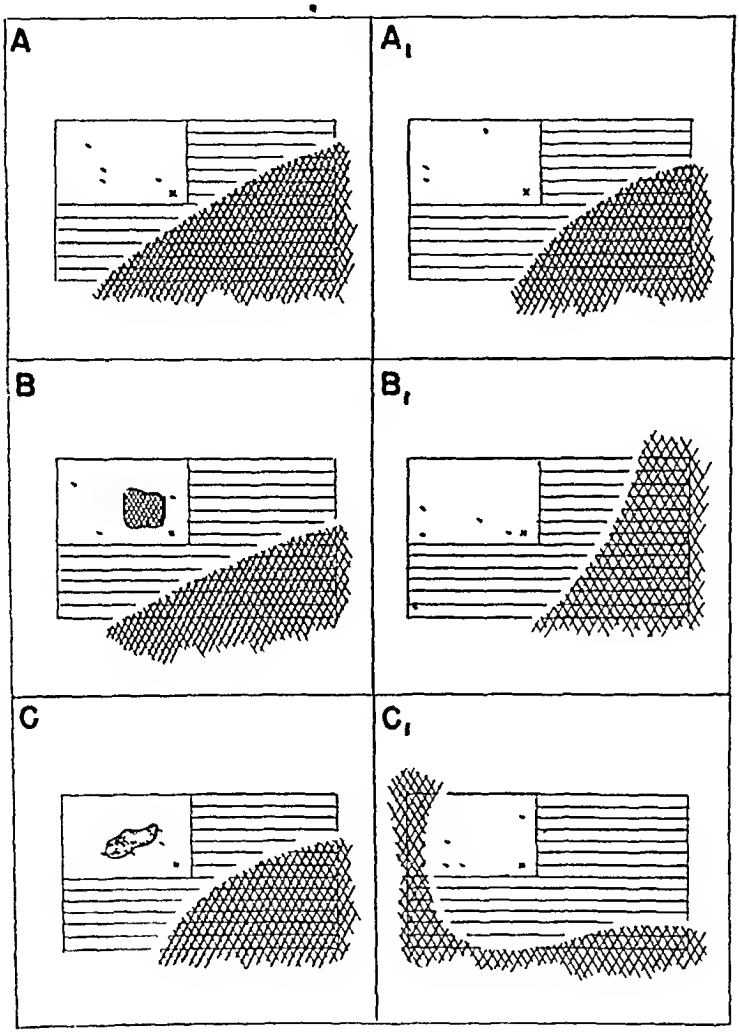

Fig 10 (case 3)—Patient's visual impressions of the American flag drawn in complementary colors (10 by 18 cm) In all instances, fixation was maintained on the star in the right lower corner of the field of stars (indicated by an *X*) 30 cm. away from the eye, under daylight illumination Shaded areas indicate parts of the flag which were invisible to the patient in the exposed flag (*A* to *C*) and in the negative after-images (A_1 to C_1) *A* indicates his impressions on fixating with both eyes, *B*, on fixing with the right eye, and *C*, on fixing with the left eye The corresponding negative after-images illustrate various degrees of completion The latter was most marked for the left eye In *B* the small shaded area indicates a region which appeared to the patient as a "dark blotch" The small stippled area in *C* denotes a region in which the stars "kept running together"

(*b*) In the after-image from the left eye the completion was most pronounced (fig 10 C_1) Only a marginal defect was seen, which surrounded the lower horizontal and the left vertical border of the stimulus pattern, apparently fusing the

two discontinuous areas of invisibility and at the same time displacing them outward

Completion on Tachistoscopic Examination—Under experimental conditions identical with those in cases 1 and 2, this patient was confronted with three series of tachistoscopic tests

TEST SERIES A The first consisted of a regular set of slides employed in testing tachistoscopic perception in patients with head trauma This series included arrays of figures and letters, geometric patterns, line drawings of objects, animals and faces, and, finally, colored slides showing complex scenes With this material, we did not find a linear, or an approximately linear, relationship between speed of exposure and amount of completion achieved At very high speeds, 1/75 and 1/100 second, the patient showed poor performance, suggestive of a generally decreased ability for rapid perception and recognition of complex patterns At very low speeds (1 second) performance was good, probably owing to scanning movements of the eyes, which could frequently be detected by direct

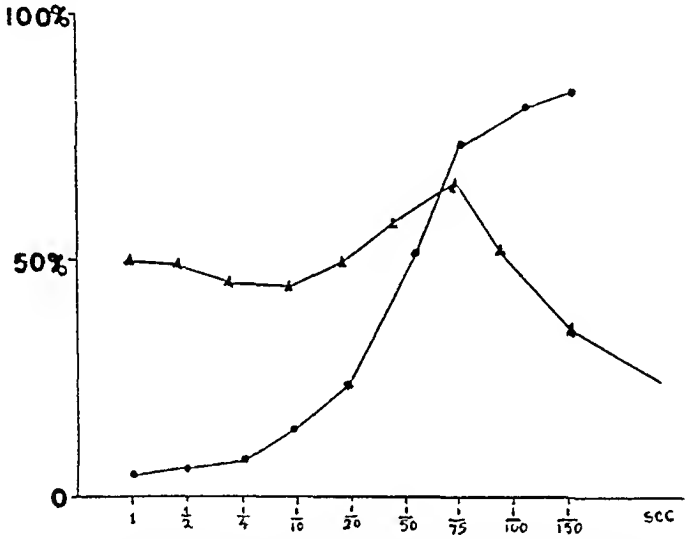

Fig 11 (case 3)—Graphs showing various degrees of "completion" on tachistoscopic examination The ordinate indicates estimated degrees of completion in terms of area, the abscissa, time of exposure Circles represent mean responses for large simple configurations, such as geometric figures, triangles, mean responses for complex linear designs, such as outlines of faces and animals Note that the simple configurations were seen best with higher speeds At high speeds, 1/100 second and above, recognition of complex designs became impossible, and outlines were ill defined At low speeds, 1/10 second and below, performance was good but was associated with scanning movements of the eyes In the intermediate range performance varied directly with speed of exposure

observation In an intermediate range, however, the effect of completion could be seen rather clearly from 1/10 to 1/50 second's exposure an increase in speed improved performance, and less and less in the patient's right field was missed (fig 11)

TEST SERIES B When tested with large simple configurations (e g, a letter H, black on white, covering most of the screen), the completion became a nearly linear function of the speed of exposure (fig 11) After-images, whenever they occurred, were reported by the patient The conditions of exposure were varied (bright and dark after-fields, presented at random) in order to minimize the

effect of the after-image on tachistoscopic recognition, and no systematic interdependence between appearance of positive or negative after-images and completion could be found

TEST SERIES C In order to analyze the factors in completion more closely, special patterns were presented which made it possible to stimulate only one quadrant, or two, or three or all four quadrants, at a single exposure A schematic summary of the more important results is given in figure 12[49]

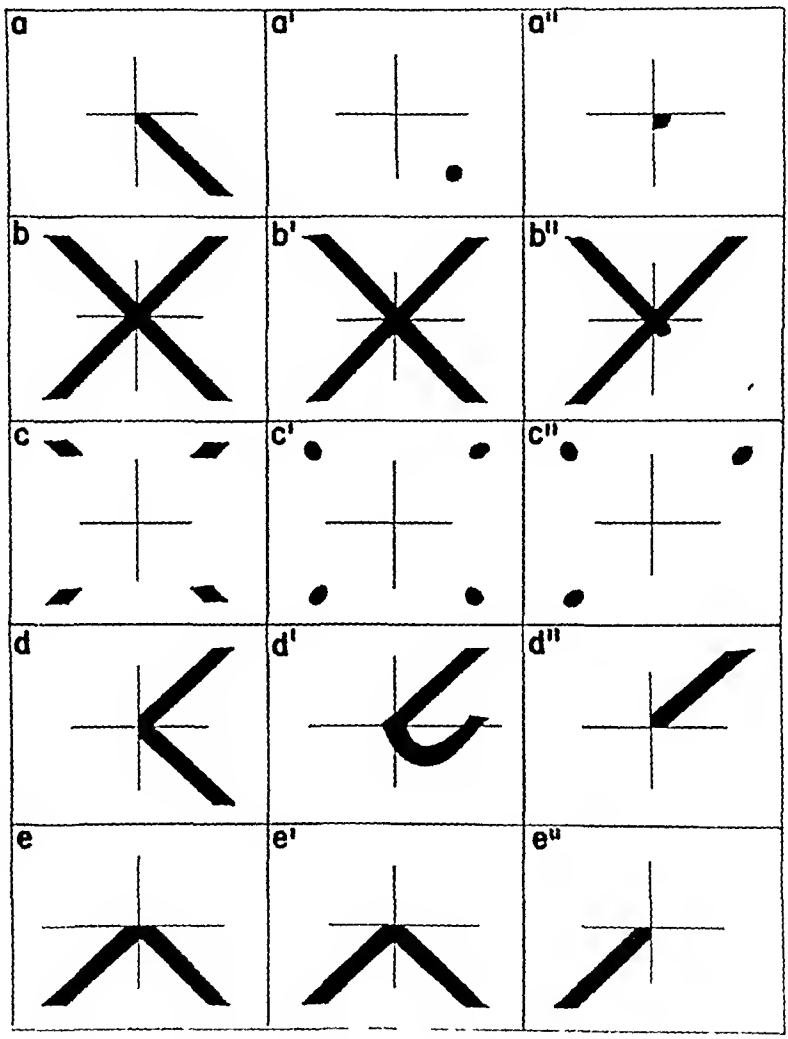

FIG 12 (case 3) —Various degrees of completion obtained on tachistoscopic examination Column 1 test patterns exposed Column 2 patient's own drawings of the pattern (as he saw it at 1/150 second's exposure), demonstrating varying amounts of completion In the right inferior quadrant shaded areas indicate a "fuzzy" appearance Note the simultaneous completion and displacement in *d'* Column 3 patient's indications of same test patterns at specified lower speeds, illustrating failure to "complete" During the test sessions the order of test patterns, as well as the succession of speeds, was at random The patient was ignorant of the number of actual configurations used

49 The patterns were produced by a large × cutt into a dark slide so that a bright figure appeared during exposure on a dark ground With different masks, one, two or three quadrants could be covered In similar fashion, the central area could be obscured so that only the four extreme tips of the ×

(Footnote continued on next page)

1 When single momentary stimulation was given in the most defective quadrant (lower right) only (fig 12*a*), the patient saw either nothing or an indistinct flash of light

2 When repeated stimulation was given under the same conditions (with random exposure of other patterns interspersed), the following results were obtained

At 1/100 second A "white square, cut off to the right" (fig 12*a*″) (no completion)

At 1/150 second A "white blur in extreme right" (fig 12*a*′) (no completion, question of displacement)

At 1/50 to 1/20 second "A rectangle in center cut off to the right" (fig 12*a*″) (no completion)

3 When the whole pattern was exposed over all four quadrants (fig 12*b*) at a speed of 1/150 second, the patient saw it whole, or almost whole, with a small gap in the lower right quadrant (fig 12*b*′) (definite completion effect) At speeds below 1/20 second the patient saw most of the area in the lower right quadrant as "cut off" (fig 12*b*″)

4 The original figure was then transformed into a four dot pattern (fig 12*c*) At a speed of 1/150 second the patient reported four dots, "one in each corner" (definite completion effect, in spite of discontinuity of pattern) At a speed of 1 second only three dots (and nothing in the lower right quadrant) were reported

5 When the left half-field was covered and the upper and lower right quadrants were exposed (fig 12*d*) (at a speed of 1/20 second and below), the patient saw only an "arrow" slanting through the upper right quadrant (fig 12*d*″) At a speed of 1/150 second he saw the same diagonal through the upper right quadrant and another line extending from the center down into the lower right quadrant, then curving back toward the upper right quadrant This lower line did not appear quite as long as the upper one (fig 12*d*′) (definite completion, with simultaneous displacement in spite of the high speed of exposure)

6 When both upper quadrants were obscured and the lower right and left quadrants exposed (fig 12*e*), the patient failed repeatedly to see anything in the lower right quadrant, even with speeds up to 1/100 second (fig 12*e*″) However, at a speed of 1/150 second he saw the diagonal through the lower right quadrant in addition to the one in the lower left quadrant and reported that only "very little" of the lower tip on the right seemed to be "cut off" (fig 12*e*′)

7 Control exposures with patterns only in one, two or three of the three quadrants exclusive of the lower right showed that the patient was not guessing Even at speeds as high as 1/150 second he did not fill in by confabulation

Comment.—This patient showed phenomena of fluctuation, extinction and completion He was also acutely aware of some of his scotomas and attributed them usually to one eye Under observation this awareness changed The subjective fields and their subsequent changes seemed to be related to the amount of extinction and completion shown in various visual tests

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were visible The presentation of the various modifications of the original pattern were made in such an order that the patient remained unaware of the fact that only one slide and one pattern were being used

Extinction appeared to be most pronounced on double stimulation and on prolonged exposure Thus, on maintained fixation on a point in the flag used for producing after-images, various areas of the test pattern were invisible These areas were different in extent in the binocular field and in the monocular fields for each eye, respectively This was contrary to the vision one would expect from the patient's perimetric fields, where the areas of scotoma were nearly congruent The differences in binocular and in monocular fields as obtained on prolonged exposure were more in keeping with the patient's subjective fields, or with his awareness of scotoma Binocularly, the scotoma in the upper left quadrant (of which the patient was still unaware at the time of these experiments) did not appear on prolonged fixation It did appear on prolonged fixation with the right or with the left eye The massive scotoma in the right lower quadrants appeared largest on binocular fixation, somewhat smaller on fixation with the right eye and smallest on fixation with the left eye It is suggested that these differences in visual fields as elicited on prolonged exposure are functions of different degrees of extinction Subjectively, the patient always felt that vision in his left eye was better, or "less obscured," than vision in his right eye Our assumption of unequal degrees of extinction might put the patient's impression on an objective basis [50]

Completion appeared in the patient's after-imagery and on tachistoscopic examination In the after-images the differences between the fields were not only maintained but proportionately increased, the smallest completion effect was noted after binocular stimulation After monocular stimulation of the right eye a somewhat larger amount was "completed," and after fixation with the left eye the completion effects were most pronounced The completion effects, as demonstrated by after-imagery, were thus much more in keeping with the patient's subjective fields of vision than were his perimetric fields

In weighing this evidence an obvious objection should be considered Since the patient had considerable difficulty in maintaining fixation, one might suspect that the completion phenomena in his after-imagery were due simply to involuntary ocular movements which carried the

50 The patient's insistence that his left eye was better (in spite of the congruence of scotomas as plotted for the left and the right eye) was probably related to the superiority of the nasal half of each retina over the corresponding temporal half According to Koellner's hypothesis,[10] there is never perfect retinal correspondence The crossed fibers in man dominate over the uncrossed fibers Thus, the left half of any binocular field is predominantly determined by the impressions supplied through the left eye This accords well with the observation that patients whose lesion is restricted to one occipital lobe (or is more severe in one occipital lobe) complain of impaired vision in the eye contralateral to the lesion

image periodically into better parts of his field The increase in the area of the after-image would then appear as a summation of various composite views gained through some kind of scanning activity However, a number of facts speak against this explanation

1 Wide variations in time of exposure did not increase or decrease the completion effect

2 Observations on after-imagery in normal subjects and in subjects with nystagmus show that ocular movements during exposure lead to suppression rather than to enhancement of after-images [50a]

3 Completion of after-images following tachistoscopic exposure could be shown in this patient to be most marked with high speeds of exposure (1/100, 1/150 second), situations into which ocular movements could not possibly have entered

Results of the various tachistoscopic examinations show the completion effect most clearly as a fairly linear function of speed of exposure whenever simple continuous patterns were being used (test series B) In contrast to observations in cases 1 and 2, and to the results in the majority of earlier cases reported in the literature [51] the patient in this case showed completion even for discontinuous dot patterns However, these patterns were regular symmetric configurations and in some ways were equivalent to continuous Gestalten (e g the four dot pattern arranged as an oblong, oriented symmetrically to the median plane)

Even with complex, meaningful stimulus patterns (arrays of letters, line drawings) some completion could be obtained, again in contrast to the results in earlier reports [52] But the distribution of results from test series A suggests that the patient's over-all performance with this material could not possibly give a simple indication of the amount of completion that could be achieved Rather, it represented a test of recognition With high speeds of exposure the patient's general "slowing" of recognition produced a considerable number of failures At low speeds the scanning movements previously mentioned disrupted the attempted control of experimental conditions In spite of this, completion appeared as a function of speed of exposure over an intermediate range of speeds

Of the results from test series C, finally, the following points should be emphasized:

(*a*) The completion effect is not obtained with any speed of exposure when only the defective quadrant itself is stimulated

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50a Bender M B, and Teuber, H L Nystagmoid Movements and Visual Perception Arch Neurol & Psychiat **55** 511 (May) 1946

51 Fuchs [8] Poppelreuter [14]

52 Fuchs [8] Poppelreuter [14] Goldstein [17]

(*b*) Completion with high speeds appears greatest on simultaneous stimulation of the most defective quadrant and of the relatively normal quadrant, such as that in the opposite half of the field

(*c*) The spatial disorientation found in the patient's lower right quadrant under ordinary conditions can be shown to occur even on tachistoscopic stimulation with speeds as high as 1/150 second If the upper and lower right quadrants are stimulated simultaneously in this situation, completion and displacement can occur at the same time [53]

SUMMARY AND CONCLUSIONS

In 3 illustrative cases of disturbances of visual fields with scotomas of varying extent and density, phenomena of fluctuation, extinction and completion were observed The three phenomena appeared to be related to each other Fluctuation was characteristic of all cases, particularly on prolonged exposure Extinction seemed to represent a more extreme form of fluctuation, since it occurred readily in areas which were otherwise characterized by fluctuation In these areas extinction could be demonstrated frequently on double simultaneous stimulation With rapid tachistoscopic exposure of patterns, the defects in the visual fields seemed to be reduced in their extent in all 3 cases This fact suggested that these field defects (though produced by circumscribed lesions) were a result of processes of extinction rather than signs of a permanent loss in function For that reason, rapid tachistoscopic exposure would prevent extinction and produce the appearance of completion Completion could thus be understood as a simple absence of "extinction"

If such dynamic processes as fluctuation, extinction and completion determine the actual (functioning) visual fields, it is unjustified to think in terms of a point for point correspondence between function and substrate The visual projection area seems to operate in an integral fashion Even circumscribed lesions do not necessarily produce functional loss of an all or none character

Widely different visual fields can be plotted for one and the same case by using different methods of field taking Even the patient's

53 Throughout the tachistoscopic examinations, only slight, if any, differences in the amount of completion were found for the binocular, the right and left fields, respectively A tendency for the left eye to obtain more completion than the right was apparent, but it was so small as to be insignificant For this reason, results for each eye and for binocular exposure were pooled in the accounts which went before When retested after he had become aware of the scotoma in the left upper quadrant (for his left eye), the patient showed definitely less completion (in the left visual field and in the binocular fields) than before Similar concomitant changes in the extent of the subjective field and the amount of completion have been reported by Fuchs [8]

subjective fields (his awareness of scotoma) may be indicative of physiologic principles which are operative in the impaired substrate

It is assumed that in such impaired tissues there is a marked lability of threshold.[17] In his discussion on Bender and Furlow's paper on Extinction,[32] Goldstein summarized his own theories by relating lability of threshold and extinction in the impaired portion of the nerve substrate to an increase in energy needed by the damaged portion of the cortex. The resultant gradient in excitability is a dynamic affair, just as normal dominance might be. That is, it is not a stable condition but a process which has to occur after each stimulation and which takes a certain time to come into play over the total cortical field in which the perceptual processes are taking place.

These spatial and temporal aspects of increased dominance would explain why extinction does not take place instantaneously on stimulation in involved and uninvolved fields. The increased fluctuation and obscuration in amblyopic regions could likewise be interpreted as an indication of a periodic recovery in the substrate's ability to function at lower thresholds.

Fluctuation, extinction and completion appear as general principles of function rather than as pathologic variations. They are brought to a focus only by the pathologic conditions. Fluctuation can be found in every normal visual field in the extreme periphery. With near threshold intensity of stimulation, it can be demonstrated also for the foveal region. Extinction and completion likewise are assumed to be processes in normal perception. Completion appears in the phenomena of Gestalt closure and "good continuation." Extinction, in particular, has usually been considered as a rare disturbance of perception in cases of injury to the brain. Our observations suggest, on the contrary, that extinction may play its role in many different field defects and that it might indeed be a feature in normal perception. It is suggested that extinction may be operative in certain phenomena of the normal visual space, such as the Aubert-Forster phenomenon. Conditions as different as the absolute hemianopsia (case 1) and the quadrant amblyopia with spatial disorientation (case 3) show similar features in respect to extinction and completion. For, under special conditions, particularly with high speed tachistoscopic exposure, images appear definitely more complete than those perceived with long exposure under conditions in which extinction would have time to take place.

Our completion effects were so striking with speeds of 1/100 to 1/150 second that (besides adducing the negative factor of absence of extinction) we are tempted to infer a positive aspect of the same central process—namely, precipitation. For at these high speeds the effect was more marked with simultaneous stimulation of the

unimpaired parts of the field than with stimulation of the involved area alone Dusser de Barenne and McCulloch [34] have shown that facilitation can be an early phase of extinction in a cortical focus and that both seem to depend on continual background activity These phenomena probably play a major role in normal reciprocal innervation In pathologic states precipitation as well as extinction can be demonstrated for cutaneous sensibilities [74] Our observations make it likely that both precipitation and extinction take place even between areas of a single visual field, in analogy to the concomitance of binocular interference and binocular enhancement

In 2 out of 3 cases, completion effects were also obtained for the patient's negative after-images, which formed after a period of prolonged fixation Observations in our series of cases are in progress which may answer the question whether "completion" in tachistoscopic exposure and in after-imagery are usually found to occur together in the same patient or whether they are readily dissociated Until more definite data are at hand regarding the incidence of completion effects under different conditions, it will be difficult to decide whether the completion effects in tachistoscopic exposure and in after-imagery have the same or different causation

The fact that after-imagery produced phenomena similar to tachistoscopic perception in our cases is difficult to explain One might assume that central components of after-images are formed suddenly after a processs of gradual summation and, while being formed, show the phenomena of irradiation into partly destroyed cortical tissues [55] But very little is known about the central components in after-imagery The complex nature of our stimulus pattern makes it unlikely that completion in the after-image was due in our cases to a simple Gestalt effect ("continuation" or "closure")

Another explanation may be considered The completed after-image is due to the very first phase of the visual stimulus It has been pointed out that the patients can see more of an object with short (1/100 second) than with long (1/10 second or more) exposures It would seem possible, therefore, that the pattern which is present in the first 1/100 second of a long exposure acts as a stimulus in the formation of an after-image Hence despite the fact that the patient sees only the smaller pattern during prolonged fixation the removal of

54 Bender [33] Reider [35]

55 "Irradiation" was originally hypothetically assumed (Plateau, cited by Duke-Elder, W S Textbook of Ophthalmology, St Louis, C V Mosby Company, 1938, vol 1 p 80) in order to explain simultaneous contrast Plateau thought in terms of spread of excitation over adjacent parts of the retina His ideas were generally abandoned (for the peripheral level) until Pieron formulated his own theory of *métacontraste* [41]

the visual stimulus results in a negative after-image of the initial, larger or more complete design

A phenomenon which may be related to the completion of visual after-images is the after-sensation experienced on removal of a stimulus when cutaneous sensory adaptation takes place Thus, when the skin becomes adapted to a continuous pressure stimulus, and after a certain interval (adaptation time) this stimulus becomes imperceptible, the removal of the stimulus even many seconds later will evoke an after-sensation, which reestablishes the original pressure percept In certain pathologic cases we found that such after-sensations exceeded the original sensation in intensity and articulateness

It should finally, be considered that completion, and other phenomena described in this communication, are not confined to visual and cutaneous perception Taken in a wider sense, they can be found to pervade the so-called higher functions, such as processes of memory and thought [42] Studies in reminiscence are a case in point The principles of function which are signalized in the phenomena of fluctuation, extinction and completion may thus have general application

1192 Park Avenue New York

News and Comment

OPPORTUNITY FOR TRAINING IN THE VETERANS ADMINISTRATION

The opportunities today for training in psychiatry and its practice present a situation unique in medicine Not only has the public become increasingly aware of the possibilities and limitations of psychiatry, but the medical profession as a whole realizes the nature of the intimate relations of its practice to psychiatry This obviously would mean an increasing load of patients in any circumstances, in addition, there is now the great number of veterans needing care This number is expected to increase

The Veterans Administration offers an opportunity to men of pioneer spirit, eager to practice their specialty in favorable circumstances Teachers are needed in the hospitals and in medical schools, seasoned men who enjoy teaching and who are interested in research and the study of methods of communicating clinical wisdom to the less experienced The patients are there The medical schools are using members of their staffs for teaching, supervision and case consultation Full time teachers are being placed in some hospitals

The administration also needs men of all types of experience who can benefit from training on the job It needs those who can organize and administer hospitals and clinics, as well as treat patients It needs residents who may have little or no formal training in psychiatry but who intend to complete their training for Board certification and to stay in neuropsychiatry

It has been attempted to make salaries throughout the neuropsychiatric service in keeping with the dignity of the medical profession Salaries range from $3,300 for the resident who is a veteran to $9,800, with 25 per cent additional compensation for those who have Board certifications

Every effort is being made to organize the work so that a minimum of time will be spent on administrative duties and paper work and the maximum with the patient This will take time to accomplish, but we are committed to this policy

The resident program is outlined as follows

1 Appointment is approved by the Deans' Committee Approval is forwarded by the Deans' Committee to the manager The manager makes the appointment The resident is placed on the payroll at the manager's office

2 Fifty per cent of the time of the resident is spent with Veterans Administration facilities

3 Veterans Administration physicians are to share in training without loss of grade when time and staff capacity permit

4 Medical schools or other sponsors of trainees are to receive appropriate tuition per resident on a yearly basis

5 Teachers are to be recompensed in the following manner

(*a*) Consultants (men of professorial or associate or assistant professorial grade) are to receive $50 per visit

(*b*) Attending physicians (men with specialty Board certification and on the teaching staffs or institutions) are to receive up to $25 a visit

Specific details on the entire neuropsychiatric program can be obtained by writing to the Veterans Administration Neuropsychiatric Service, Washington 25, D C A list of medical schools now receiving applications for resident training follows

Medical School	Veterans Administration Institution	Applications Received by
University of California Medical School Stanford University School of Medicine	Palo Alto, Calif	*Dr Karl Bowman, University of California Medical School, San Francisco
University of Southern California School of Medicine College of Medical Evangelists	Sawtelle, Calif	*Dr Samuel Ingham, 727 West Seventh Street, Los Angeles
University of Louisville School of Medicine	Nichols General Hospital	*Dr S Spafford Ackerly, University of Louisville School of Medicine, Louisville Ky
University of Michigan Medical School	Fort Custer, Mich	Dr Raymond Waggoner, University of Michigan Medical School, Ann Arbor, Mich
University of Minnesota Medical School	St Cloud, Minn	Dr Donald Hastings, University of Minnesota Medical School, Minneapolis
Cornell University Medical College	Bronx, N Y	Dr Oscar Diethelm New York Hospital, New York
Long Island College of Medicine	Northport, N Y	Dr Howard Potter, Long Island College of Medicine Brooklyn
New York University College of Medicine	Mental Hygiene Clinic	Dr Samuel Wortis, Bellevue Hospital New York 16
Duke University School of Medicine	Mental Hygiene Clinic	*Dr Maurice Greenhill Duke University School of Medicine, Durham N C
University of Oregon Medical School	American Lake	Dr Henry Dyson, University of Oregon Medical School, Portland, Ore
University of Pennsylvania School of Medicine Temple University School of Medicine Jefferson Medical College of Philadelphia	Coatesville, Pa Lyons, N J	*Dr Edward Streeker University of Pennsylvania School of Medicine, Philadelphia
Boston University School of Medicine Tufts College Medical School Harvard Medical School	Mental Hygiene Clinic, West Roxbury Mass	*Dr Harry C Solomon Harvard Medical School Boston
University of Wisconsin Medical School	Mendota, Wis	*Dr W F Lorenz University of Wisconsin Medical School, Madison Wis
University of Colorado School of Medicine	Mental Hygiene Clinic	Dr Franklin Fbaugh, University of Colorado School of Medicine, Denver
Western Reserve University School of Medicine	Crile General Hospital	Dr Douglas Bond Western Reserve University School of Medicine Cleveland
	Winter General Hospital, Topeka Kan	Dr Karl Menninger, Winter General Hospital Topeka, Kan

* Chairman of Neuropsychiatric Sub Committee of Deans' Committee

AMERICAN BOARD OF NEUROLOGICAL SURGERY

During the war, in order to cooperate with the surgeons general of the Army and Navy in the classification of specialists, the American Board of Neurological Surgery permitted applicants whose training was satisfactory to take their examination before complying with the requirement of two years' independent practice of neurologic surgery In no instance, however, was the Board's certificate issued until all requirements had been fulfilled At its last meeting in Nashville, Tenn, on April 7, 1946, the Board voted to return to its prewar practice, and in the future no candidate will be examined until he has complied with all requirements of the Board as to both training and practice However, the Board invites prospective candidates to submit their qualifications to the Board when their period of training is completed and before they have begun their period of practice

Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

Physiology and Biochemistry

THE OXYGEN CONTENT OF CEREBRAL BLOOD IN PATIENTS WITH ACUTE SYMPTOMATIC PSYCHOSES AND ACUTE DESTRUCTIVE BRAIN LESIONS HAROLD E HIMWICH and JOSEPH F FAZEKAS, Am J Psychiat **100** 648 (March) 1944

Himwich and Fazekas studied the difference in oxygen content of arterial and of internal jugular venous blood in a case of each of the following disorders pernicious anemia with mental symptoms, cardiac decompensation with psychosis and psychosis associated with acute syphilitic encephalitis In cases of the first two the venous oxygen levels were subnormal, indicating an inadequate cerebral oxygen supply, due in the case of pernicious anemia to decreased oxygen-carrying capacity of the blood and in the case of cardiac decompensation to slow cerebral blood flow In the case of acute syphilitic encephalitis the venous oxygen level was above normal and the difference in oxygen content of venous and of arterial blood was less than normal This was interpreted as due to a decrease in removal of oxygen from the blood as a result of the decrease in viable brain tissue

Himwich and Fazekas state that determination of the oxygen content of the cerebral venous blood may serve to indicate that mental symptoms are produced by inadequate oxygen supply or that they result from changes within the brain It is necessary to rule out alterations in the rate of cerebral blood flow

FORSTER, Philadelphia

CARBONIC ANHYDRASE IN MAMMALIAN TISSUE W ASHBY, J Biol Chem **151** 521, 1943

The purpose of this investigation is primarily to study the distribution of carbonic anhydrase in the central nervous system, the results of which will be given in subsequent papers The present paper deals with an exploration of the possibilities of the technic previously described by use of tissues, some of which, like those of the central nervous system, do not have specific excretory or secretory functions with respect to carbon dioxide, the hydrogen ion or the CO_3 anion The aim has been to establish an orientation toward the function of the carbonic anhydrase found in the central nervous system The carbonic anhydrase content of the following tissues has been studied with the technic previously described, by which the carbonic anhydrase activity of the tissues can be distinguished from that of the contained blood kidney, divided into medulla and cortex, liver, human striated muscle, adrenal gland, rat embryo, and brain In the human kidney the enzyme content of the cortex was higher than that of the medulla The medulla contained variable amounts of the enzyme In this series of human muscle, low activity was associated with malignant growths, tuberculosis and extreme old age, and activity was greater after a comparatively rapid death Variations in results both between species and between individuals were also noted in other tissues In contrast to the results for the aforementioned tissues, no activity was found in the adrenal gland or in the rat embryo, while an activity approaching 10 per cent of that of the blood was found as a maximum in the central nervous system of 8 species of animals studied The possible significance of carbonic anhydrase in the brain is discussed

PAGE, Cleveland

THE PATTERN OF DISTRIBUTION OF CARBONIC ANHYDRASE IN THE CEREBRUM OF MAN COMPARED WITH THAT OF CERTAIN OF THE LOWER ANIMALS W ASHBY, J Biol Chem **156** 323, 1944

In the hog, the dog and the cat a greater amount of carbonic anhydrase has been found in the cortex than in the white matter immediately below it An average ratio of 34 9 22 5 was found in 20 series tested In the human brain, as a rule, more carbonic anhydrase was found in the white matter immediately below the cortex than in the cortex This was the relationship in 81 series from 18 brains Exception to this excess was found in the motor area of the human brain, where the relationship was that found in the animal brains

PAGE, Cleveland

ON THE DISTRIBUTION OF CARBONIC ANHYDRASE IN THE CEREBRUM W ASHBY, J Biol Chem **156** 331, 1944

In previous papers data were presented indicating that carbonic anhydrase tends to have a pattern of quantitative distribution in the central nervous system somewhat peculiar to the species studied but, in general, shows an increase rostrally In the dog, the cat and the hog a steep gradient of increase was found from the brain stem to the pallium In man this was apparently not the case, the average content of the pallium being equal to or less than that for the rostral end of the pons Man also differed from the aforementioned animals in that, except in the motor area, the maximum carbonic anhydrase content of the pallium was found immediately below the cortex, while in the animals studied it was found within the cerebral cortex It was postulated that the carbonic anhydrase in the tissues of the central nervous system might play a part in determining the speed with which energy was made available for conduction of nerve impulses and might therefore determine dominance of an area and the degrees of radiation of an impulse Further data are added on the amount of carbonic anhydrase in the human pallium They support the belief of Ashby that there is a parallelism between mental function and carbonic anhydrase content The pattern of intensity of activity seen in the electroencephalogram shows a good correlation with the patterns found for carbonic anhydrase

PAGE, Cleveland

STUDIES ON CHOLINE ACETYLASE I EFFECT OF AMINO ACIDS ON THE DIALYZED ENZYME, INHIBITION BY α-KETO ACIDS D NACHMANSOHN and H M JOHN, J Biol Chem **158** 157, 1945

Recent investigations have provided evidence that the release and removal of acetylcholine is an intracellular process connected with the nerve action potential According to a new concept, the active ester depolarizes the neuronal membrane by rendering it permeable to all ions In a resting condition the membrane is selectively permeable to potassium Flow of current is thus generated (action potential), which stimulates the adjacent region There the process is repeated and the impulse in this way propagated along the axon The properties of the enzyme choline acetylase, which forms acetylcholine under strict anaerobic conditions in the presence of adenosine triphosphate, have been further investigated In extracts obtained from rat or guinea pig brain, 100 to 150 micrograms of acetylcholine may be formed per gram per hour The optimal rate decreases rapidly after fifteen minutes of incubation Adenosine triphosphate is split, in spite of the presence of fluoride, at a rather high rate 'An initial concentration of 3×10^{-3} molar is optimal. At this concentration the nucleotide is not the limiting factor of the reaction The enzyme requires potassium ions The optimal concentration has been found to be near 0 08 molar, which is approximately that found in mammalian brain On dialysis the enzyme becomes inactive In two hours it has lost 80 to 85 per cent of its original activity Addition of potassium reactivates it only partially Further, reactivation may be obtained with glutamic acid Only the natural *l* (+) form is effective The *d* (—) form has practically no effect

Cysteine is still more effective than glutamic acid and may reactivate the enzyme almost completely When combined with cyanide, glutamic acid has an effect almost as strong as cysteine Of all other amino acids tested, only *l* (+)-alanine enhances the activity of the dialyzed enzyme to a notable degree, but not so much as glutamic acid The other amino acids have either a weak effect or none Dicarboxylic acids have no effect on the dialyzed enzyme Citric acid reactivates it almost as strongly as does glutamic acid, α-keto acids inhibit the enzymes in 10^{-3} to 10^{-4} molar concentrations Pyruvic, phenylpyruvic, hydroxyphenylpyruvic and α-ketoglutaric acids were tested No inhibition was found with acetoacetic acid In extracts prepared from powder of acetone-dried brains, choline acetylase has lost only a small fraction of its original activity Cholinesterase may be almost completely inactivated by treatment with acetone In this way the two enzymes may be separated

PAGE, Cleveland

THE EFFECT OF OXYGEN TENSION ON THE METABOLISM OF CEREBRAL CORTEX, MEDULLA AND SPINAL CORD FRANCIS N CRAIG and HENRY K BEECHER, J Neurophysiol **6** 135 (March) 1943

Craig and Beecher studied the rates of oxygen uptake and anaerobic lactic acid production of slices of cortex, medulla and spinal cord The oxygen uptake in all three tissues was found to be sensitive to oxygen tension The shape of the oxygen uptake–oxygen tension curve was essentially the same for all three tissues Anaerobic lactic acid production was twice as great in the cortex as in the medulla and was sensitive to oxygen tension in the cortex and medulla but not in the cord In the cortex, lactic acid production and oxygen uptake varied inversely when the oxygen tension was altered In the medulla lactic acid production was maximal at 2 to 3 volumes per cent of oxygen

FORSTER, Philadelphia

PROPAGATION OF EPILEPTIFORM IMPULSES IN THE BRAIN IV ROLE OF SUBCORTICAL STRUCTURES S OBRADOR ALCALDE, Bol d lab de estud med y biol **1** 145 (Aug) 1942

Obrador Alcalde observed convulsive movements and tonic contractions on stimulating the white substance in cats after extirpating the motor area The responses to electrical stimulation of the subcortical white substance were different in character from the reaction to electrical stimulation of the cortex, and higher voltages were necessary to elicit reactions

In some cases of stimulation of the basal ganglia after extirpation of the cerebral hemisphere the only responses were autonomic In other cases stimulation of the basal ganglia caused tonic contractions with flexion and extension of the extremities, especially those contralateral to the side stimulated, stronger stimulation caused superimposed clonic contractions, and on a few occasions a complete epileptic attack, similar to that seen with intense cortical stimulation, was elicited The more intense stimuli probably diffused into neighboring, and even distant, structures It is difficult to evaluate these experiments because they were done soon after cerebral extirpation, and not enough time had elapsed for degeneration of the pyramidal tracts It was noted at times that the convulsive movements disappeared immediately after stimulation was stopped This indicated probable stimulation of projection system fibers, since gray cortical matter has more capacity for automatic activity and after-discharge

Electrical stimulation of subthalamic and hypothalamic regions in some cases caused typical autonomic responses, such as pupillary dilatation, contraction of the nictitating membranes and evacuation of the bladder In animals under light anesthesia, stimulation of these regions caused excitement, aggressive behavior, mewing, and the like At times stimulation of these regions caused progression movements of the extremities, violent convulsions were noted with more intense stimulation The author observed the typical tegmental response of Graham

Brown on stimulating the surface of the brain stem of decerebrate animals This pattern appeared even when the pyramidal tracts in the bulb were sectioned In addition to this classic response, the author noted generalized tonic responses in the limbs He concludes that the generalized convulsion represents the result of physiologic interrelationships at various levels of the neuraxis

SAVITSKY, New York

Neuropathology

PRIMARY SARCOMATOUS MENINGIOMA (PRIMARY SARCOMA OF THE BRAIN) JOSEPH H GLOBUS, SIDNEY LEVIN and JACK G SHEPS, J Neuropath & Exper Neurol **3** 311 (Oct) 1944

Globus, Levin and Sheps surveyed 150 cases of meningioma, histopathologic study revealing a sarcomatous change in 16 (9 3 per cent) Eight of these cases are included in the present study

Primary sarcomatous meningiomas usually occur in the first two decades of life Both sexes are equally represented, and the disease usually runs a clinical course of about six months Headache was present in all but 1 case and papilledema in 4 of the 8 cases Primary atrophy of the optic nerve was present in 2 cases, and the disks were normal in 2 cases Generalized convulsions occurred in 2 cases, and stiff neck and the Kernig sign were present in 4 of the 8 cases Root pain was present in 4 of the 8 cases, in 2 it was an initial symptom Surgical intervention afforded only temporary improvement in 5 of 8 cases Roentgen irradiation also brought only transient relief in 4 cases In 2 cases there was clinical evidence of multiple lesions, and tumor cells were recognized in the cerebrospinal fluid

The authors identified 7 of the 8 tumors specifically as sarcomatous pial meningiomas and 1 as a sarcomatous leptomeningioma The right cerebral hemisphere was the site of the tumor in 3 cases, and the cerebellum, with or without dissemination, in 2 cases, in the same number diffuse and primary involvement of the meninges had occurred The meninges were partly involved in all the other 6 cases The choroid plexus was the seat of sarcomatous formation in 1 case Multiple tumors in all the cranial fossae were found in 1 case, with the largest mass in the parietal lobe In 1 instance metastasis of the primary pial sarcoma into the regional lymph nodes was definitely ascertained The cells of this tumor are usually undifferentiated, small, oval cell aggregates along a blood vessel Giant cells are frequent among the cellular elements but are not essential for diagnostic purposes Connective tissue is present in all the tumors The cellular constituents are commonly traceable to derivatives of the pial component of the leptomeninges Sarcomatous meningioma may give rise to visceral metastasis

GUTTMAN, Philadelphia

HERPETIC MENINGO-ENCEPHALITIS GEORGE B HASSIN and I A RABENS, J Neuropath & Exper Neurol **3** 355 (Oct) 1944

Hassin and Rabens report the case of a 48 year old white man who had a cluster of vesicles "characteristic of herpes zoster" over the left frontal region About sixteen days after the onset of his illness he became increasingly dazed and apathetic, and singultus developed and persisted The temperature became elevated, and urinary retention ensued His condition worsened, he became irrational, lapsed into coma and died about twenty-two days after the onset of his illness The clinical diagnosis was herpetic encephalitis

Neuropathologic study revealed vascular and widespread degenerative changes (degenerative nonvascular softening) in the subcortex and especially in the pons, medulla and cornu ammonis There was associated meningitis of both the vertex and the base of the brain, including some of the cranial nerves Changes in the nerve cells were generally mild, but the nucleoli exhibited tinctorial changes and

occasionally appeared vacuolated The absence of all inclusions does not speak against the herpetic nature of encephalitis

The abnormalities differ from those seen with encephalitis lethargica of the von Economo type, trypanosomiasis, the cerebral forms of poliomyelitis and typhus, but resembled the St Louis type of epidemic encephalitis, equine encephalomyelitis and Borna disease of horses

A diagnosis of the specific form of encephalitis cannot be made from neuropathologic study without a knowledge of the history or/and additional laboratory tests, such as animal inoculations and immunologic observations

GUTTMAN, Philadelphia

Psychiatry and Psychopathology

THE ROLE OF THE PREMORBID PERSONALITY IN ARTERIOSCLEROTIC PSYCHOSES DAVID ROTHSCHILD, Am J Psychiat **100** 501 (Jan) 1944

In studying the clinical and anatomic relationships in patients with arteriosclerotic psychosis, Rothschild found many inconsistencies, indicating that different persons vary greatly in their ability to withstand cerebral damage In only a minority of the patients was the damage of such degree that the quantitative factor could be considered all important Rothschild found that persons who are in any way handicapped psychologically are highly vulnerable to the development of arteriosclerotic psychoses Many of his patients displayed inadequate personalities, and less frequently situational stress was noted He concludes that, while organic cerebral damage can produce a psychosis in any one, the anatomic factor is all important in only a minority of cases and that in the majority of arteriosclerotic psychoses responsibility is shared by personality factors

FORSTER, Philadelphia

AGE AND ELECTROENCEPHALOGRAPHIC ABNORMALITY IN NEUROPSYCHIATRIC PATIENTS MILTON GREENBLATT, MARIE M HEALEY and GERTRUDE A JONES, Am J Psychiat **101** 82 (July) 1944

Greenblatt studied the electroencephalograms of 1,593 neuropsychiatric patients and 240 control subjects Ten per cent of the control group had abnormal records Rhythms of 8 to 12 per second were considered normal, and abnormal rhythms were divided into slow, fast and mixed slow and fast Pronounced alterations during hyperventilation were also considered abnormal The percentages of abnormalities associated with various neuropsychiatric disorders were as follows alcoholic psychosis, 22 per cent, schizophrenia, 23 per cent, psychopathic personality and behavior disorders, 31 per cent, manic-depressive psychosis, depressed type, 31 per cent, psychoneurosis, 34 per cent, manic-depressive psychosis, manic type, 42 per cent, psychosis with mental deficiency, 50 per cent, involutional psychosis, 51 per cent, and senile and arteriosclerotic psychoses, 54 per cent With involutional psychosis and manic-depressive psychosis, depressed type, there was a large amount of fast activity, while with senile and arteriosclerotic psychoses, psychosis with mental deficiency, psychopathic personality and behavior disorders there were large amounts of slow activity Greenblatt found the incidence of abnormalities correlated with the age of the patient, the highest incidence occurring in youth and old age and the lowest between 25 and 45 years of age The incidence of slow activity decreased between the ages of 15 and 45 to 55 and rose again, while the incidence of fast activity increased within the same range and then declined Greenblatt concludes that the changes in the electroencephalogram associated with the aforementioned neuropsychiatric conditions are largely explained by variations in age

FORSTER, Philadelphia

WAR NEUROSIS IN THE ARMY AND IN CIVILIAN LIFE TIKHON I YUDIN, Am Rev Soviet Med **1** 544 (Aug) 1944

Yudin discusses observations on various forms of barotraumatic illness, emotional shock and hysterical reactions, all of which followed bombings and presented a variety of problems of evacuation and therapy

In the barotraumatic conditions the stunning of consciousness is in the nature of Bleuler's "graduated weakening of consciousness," in that a certain insignificant part of the perceptions is retained and there are a few bridges connecting the patient with reality After severe contusion or destruction of brain substance the very continuity of consciousness is broken A subject suffering from barotrauma may be comatose, but muscular tone is preserved After cerebral contusion the body is flaccid, and soon the patient begins to moan from pain, his face betrays suffering, excitement and twitching are not rare In emotional shock or hysteria the patient rarely falls to the ground The pupils are dilated if there is an initial stuporous state, it disappears rapidly Questioning elicits a detailed description of the experience during the bombardment

Yudin distinguishes three forms of barotraumatic reactions All three forms require complete rest at the beginning of the illness, but each calls for a different therapeutic approach Cerebrospinal hypertension requires punctures and ultrashort wave therapy The author recommends iodine iontophoresis for the vascular type The persistent defects in the hypertensive patients usually bore the character of prolonged apathy, while the vasopathic patients displayed mild euphoria When "hysterical fixations," such as deaf-mutism appear, ether narcosis and psychotherapy are employed At first almost all the patients show deaf-mutism, with easy fatigability of sight and altered perception of pain Depending on the initial trauma, this state persists for one to three weeks and is followed by asthenia without irritability and with subsequent recovery With the more severe trauma this course takes from two to three months

The patients are evacuated quickly to special hospitals and are not retained in general hospitals Immediate therapy resulted in a recovery rate of 93 per cent of the deaf-mute patients in the author's series The remaining 7 per cent had for the most part, organic changes in the auditory apparatus When symptoms of hysteria persist despite treatment, the patient is sent to work under civilian conditions

The incidence of neuroses, and even psychoses, diminished among the civilian population during the war Data indicate that the number of neuroses increased only among women in the climacteric period and among males suffering from arteriosclerosis However, the incidence of the neuroses was reduced as far as possible through care of the families of the front line fighters the widespread distribution of care in dispensaries and relief of women over 50 from the need to work

GUTTMAN, Philadelphia

RORSCHACH METHOD AND PSYCHOSOMATIC DIAGNOSIS PERSONALITY TRAITS OF PATIENTS WITH RHEUMATIC DISEASE, HYPERTENSIVE CARDIOVASCULAR DISEASE, CORONARY OCCLUSION, AND FRACTURE C KEMPLE, Psychosom Med **7** 85 (March) 1945

Kemple made Rorschach studies of patients between the ages of 15 and 50 years who had been admitted to the hospital with rheumatic disease, hypertensive cardiovascular disease, coronary occlusion or fracture The studies showed that there were certain characteristic personality trends associated with each of the illnesses, and the results were in agreement with those of previous research studies using other clinical methods

The Rorschach tests showed that patients with rheumatic disease are characteristically passive, masochistic, instinctively weak and infantile, with an underlying hysteria Patients with hypertensive disease are more ambitious for power and have more conscious hostility, and their aggressions and their more dominant passive, dependence needs are more constantly in acute conflict Obsessive-com-

pulsive defenses are conspicuous and the patients are more introversive Patients with coronary occlusion are more aggressive and more striving for power and prestige They are more dependent on external achievement for satisfaction and security and express a great deal of emotion outwardly Patients with fracture fall into three groups introversive, constricted and extratensive In all the groups there is an effort to compromise between passivity and aggression, with a marked emphasis on self determination, independence and day to day pleasure

These studies indicate that the patient whose personality resembles that associated with a given illness is more likely to have organic damage the more he diverges from psychologically healthy norms and the more he manifests a lack of protective defense mechanisms

WERMUTH, Philadelphia

AN EXPERIMENTAL STUDY OF THE FUNCTIONS OF THE FRONTAL LOBES IN MAN G K YACORZYNSKI and LOYAL DAVIS, Psychosom Med **7** 97 (March) 1945

Yacorzynski and Davis tested 5 patients who had undergone unilateral frontal lobectomy (1 patient with a lesion of the left lobe and 4 patients with lesions of the right lobe) by experimental procedures and compared results with those for 8 normal controls A number of differences were found between the two groups 1 The patients with lesions of the frontal lobe required a longer time and more illumination to perceive geographic figures and words than did the controls 2 They did not perceive as many meaningful objects in ambiguous figures 3 The illusory effect of the Muller-Lyer Illusion, measured quantitatively, was exaggerated, and the illusory effects of many other visual illusions were not perceived 4 They were not able to recall as many objects exposed visually 5 They did not perceive reversals on many of the figures with reversible perspectives On the basis of these results, the authors postulate that after unilateral frontal lobectomy (1) a longer time is required to perceive a stimulus, (2) the number of situations which are perceived in a stimulus field is decreased, (3) there is inability to shift readily from one stimulus to another and (4) there is a distortion of normal perceptions

Other forms of atypical behavior in these patients were noted Euphoria was present in 2 of the subjects, and the patient with the lesion of the left frontal lobe showed unmistakable symptoms of aphasia Immediate memory was apparently not affected

WERMUTH, Philadelphia

ACUTE NICOTINIC ACID DEFICIENCY (ANIACINOSIS) B GOTTLIEB Brit M J **1** 392 (March 18) 1944

Gottlieb believes that the lives of many middle-aged and elderly persons exhibiting mental confusion of undetermined cause could be saved by the prompt administration of nicotinic acid The condition, probably nicotinic acid deficiency, may be manifested by mental confusion, delusions, hallucinations, stupor, manic excitement and confabulations In most cases no other evidence of vitamin deficiency except pellagra, thiamine deficiency, ophthalmoplegia or scurvy is found Of diagnostic importance are the dietetic history, a history of chronic alcoholism and response to treatment with nicotinic acid Treatment consists of the administration of 100 mg of nicotinic acid or 30 mg of nicotinamide hourly for ten doses in the first two days by mouth or stomach tube, followed by administration of 500 mg of nicotinic acid daily for a few more days in five doses and then a residual dose of 25 mg three times a day In addition, Marmite (extract of yeast containing the vitamin B complex), ½ ounce (15 Gm), or Bemax (preparation of the seed germ of certain cereals containing vitamin A, thiamine, riboflavin and vitamin E), 1 to 2 ounces (31 to 62 Gm), daily, and thiamine hydrochloride, 25 mg a day, are given The patient should be placed on a good mixed diet as soon as possible

ECHOLS, New Orleans

REHABILITATION OF THE NEUROTIC LOUIS MINSKI, J Ment Sc 89 390 (July-Oct) 1943

Minski points out that, in his opinion, it is easier to rehabilitate a patient who has suffered from an acute or a recurrent psychosis than it is to rehabilitate the neurotic patient The illness of the psychotic patient runs a well defined course, but the neurotic patient may have long-drawn-out symptoms, perhaps exaggerated when he returns to work

The greater number of patients admitted as neurotic to a military emergency hospital were those who should never have been allowed in military life, men who were sick before enlistment or almost so

But many neurotic persons in the service are merely miscast in their particular job and can be rehabilitated by replacement in a more congenial position This is also true of men for whom strenuous duties are too much but who can fill in at less arduous tasks

The author describes the procedure in an annex of 200 beds attached to the hospital Neurotic patients whom it was decided to return eventually to the service were admitted there in uniform, without the somewhat demoralizing influence of wearing "hospital blues" They were given occupations of the heavier types and vigorous physical training They greatly appreciated the change in dress, i e, from "blues" to uniform

Rehabilitation of the neurotic patient involves not only hospital care, with psychotherapy and occupational therapy and discharge, but resettlement in civilian life It is the body of chronic neurotic patients who are of the most concern here, for, although most of them may have civilian jobs during the war, in peacetime they will not survive competition with healthier brethren It is for these that the author suggests the establishment of colonies of neurotic patients where the members live and work with their families on an almost self-supporting basis, plus, perhaps, a government subsidy No disadvantage would be suffered by having so many neurotic persons together, because, in the author's opinion, the neuroses are dependent more on environment than on heredity and the former would be adjusted to the best interests of all Although the plan would be more expensive at first, in the long run it ought to be cheaper, since it should help to eliminate neurosis, especially when combined with voluntary sterilization if the disease has a hereditary factor

McCARTER, Boston

Diseases of the Brain

FREQUENCY OF CONVULSIVE DISORDERS IN FEEBLEMINDED R W WAGGONER and J G SHEPS, Am J Psychiat 100 497 (Jan) 1944

Waggoner and Sheps maintain that the close relation of convulsive disorders to feeblemindedness is largely due to the presence of many mentally deficient patients in institutions for epileptic patients The authors therefore studied the incidence of convulsive states in mentally deficient persons They collected 254 persons with mental deficiency of all types except that associated with congenital syphilis who had lived at least one year and who presented gross or microscopic cerebral lesions Of this series of 254 patients 105, or 41 34 per cent, had convulsive attacks Of patients with the exogenous, or acquired, type of mental deficiency 51 per cent had convulsive disorders, whereas of patients with the endogenous type 39 per cent were thus afflicted The authors found no difference in the incidence of convulsive disorders in the various clinical subdivisions of the endogenous type They stress the infrequency with which convulsions are associated with mongolism Investigation revealed an incidence of epilepsy in 3 7 per cent of the parents of patients with convulsive disorders and no epilepsy in the parents of those without seizures

FORSTER, Philadelphia

INTRACRANIAL DURAL CYST WEBB HAYMAKER and MILES E FOSTER JR, J Neurosurg **1** 211 (May) 1944

Although cysts spatially related to the dura mater have been occasionally reported, only one cyst located solely within the dura has been described, and all the cysts were in the spinal canal Some of the epidural cysts seemed to be dural diverticula, while others appeared to be herniations of arachnoid through congenital dural defects

Haymaker and Foster report a case of excruciating headache and blurred vision associated with a large defect in the occipital bone Craniectomy revealed an intradural cyst of the posterior fossa, containing 100 cc of fluid The patient died of complicating meningitis Autopsy demonstrated that both walls of the cyst were composed of dura The authors suggest that congenital failure of fusion was responsible for formation of the cyst

WHITELEY, Philadelphia

A CASE OF CONGENITAL ATRESIA OF THE FORAMINA OF LUSCHKA AND MAGENDIE SURGICAL CURE A EARL WALKER, J Neuropath & Exper Neurol **3** 368 (Oct) 1944

Walker reports the case of a 20 year old woman who had always had a large head, weakness of the right extremities and unsteady gait There was a five year history of headaches and fainting spells, usually at the time of the headaches, and in one of these attacks the patient is said to have had clonic movements of the extremities There were no other abnormal physical or neurologic signs The correct diagnosis was made clinically on the basis of the roentgenograms of the skull, which revealed that the lateral sinus was conspicuously elevated and the posterior fossa was, accordingly, enormously enlarged A suboccipital craniectomy was performed and an opening made in the fourth ventricle Surgical removal of the membrane from the posterior margins of the rhomboid fossa relieved all symptoms, and the patient returned to work This is the third case to be reported in which the patient survived operation

GUTTMAN, Philadelphia

PROLONGED DISTURBANCES OF CONSCIOUSNESS FOLLOWING HEAD INJURY BURNESS E MOORE and JURGEN RUESCH, New England J Med **230** 445 (April 13) 1944

Moore and Ruesch report studies on 39 patients with prolonged disturbances of consciousness, such as coma, semicoma, confusion, delirium, stupor, drowsiness and dysphasia, which persisted seventy-two hours or more after a head injury This group of patients represents 8 per cent of all persons with head injuries admitted to the Boston City Hospital during a six month period The authors analyzed the histories and the frequency and duration of abnormal medical, neurologic and psychiatric symptoms and signs and made an evaluation of various pertinent laboratory studies

All the patients were examined within two hours after the accident The duration of hospitalization ranged from four to sixty-two days, with an average of twenty-nine days After discharge the patients were kept under observation, whenever possible, at home or in the institutions to which they had been transferred There were 31 males and 8 females Their ages ranged from 6 to 72 years, with an average of 39 years Twenty patients (51 per cent) were within the fourth and fifth decades of life Twenty-three patients (60 per cent) were addicted to alcohol From the psychiatric viewpoint, 21 patients (54 per cent) were classified as psychopathic personalities Eighteen patients (46 per cent) acquired their head trauma from a fall, while traffic accidents were responsible for the next largest group, of 14 patients (36 per cent) A variety of incidents accounted for the trauma of the remaining 7 patients (18 per cent)

On the basis of the high incidence of such observations as alteration in the electroencephalographic pattern, fracture of the skull, blood in the spinal fluid with

increased pressure and a Babinski sign, the authors concluded that the prolonged mental confusion is associated with severe damage to the brain The vital signs were significantly altered in about one-half the cases and appeared to be independent of the presence and duration of confusion During the period of hospitalization immediately following injury, intellectual disturbances outnumbered other mental abnormalities Emotional disorders tended to appear later than the cognitive dysfunctions and persisted longer, they were frequent even in cases of short confusion

Ability to speak returned on an average within the first day The first response to psychologic tests appeared during the second week, before correct orientation for place, situation and time, which returned in that order Drowsiness and restlessness held no fixed place in the order of recovery, and appeared to be independent of the course of recovery of intellectual function

Gross intellectual defect persisted for six months in 31 per cent of the patients, and in each patient it was preceded by a period of confusion lasting longer than nineteen days

The duration of disorientation proved to be one of the most reliable and easily obtainable criteria of the seriousness of mental disability The total duration of post-traumatic amnesia is directly related to the period of disorientation and thus has equal value but is obtainable only later, and is then a purely subjective quantity

GUTTMAN, Philadelphia

A FORM OF PRESENILE DEMENTIA WITH SPASTIC PARALYSIS C WORSTER-DROUGHT, J G GREENFIELD and W H MCMENEMEY, Brain 67 38, 1944

Worster-Drought, Greenfield and McMenemey report the observations at autopsy in an additional member of their previously described family, which was characterized by the occurrence of presenile dementia with spastic paralysis The patient was a woman aged 51 who had defective memory, impaired intelligence disorientation, apathy and difficulty in attention, together with spasticity of all four extremities and some incoordination The illness was of nine years' duration, during which time both the mental changes and the paralysis increased

On gross examination, the brain and the spinal cord seemed normal Section of the cerebral hemispheres revealed a diffuse grayish degeneration of the centrum semiovale Histologic examination of the central nervous system revealed changes similar to those previously described by the authors in another member of the same family These changes consisted of (1) extreme hyaline thickening of the media of the small arteries of the meninges and of the parenchyma, both of the brain and of the spinal cord, and (2) the presence of peculiar plaquelike structures, often around small blood vessels and most abundant in the cornu ammonis and the cerebellar cortex Many of the vessels showing the degeneration of the media were surrounded by a narrow zone of rarefaction, and a few had a narrow zone of lymphocytes Both blood pigment and hemorrhage occurred about some of the degenerated vessels The arteriolar changes were unlike those seen in hyperpiesis Wedge-shaped scars and areas of neuronal change in the cortex were ascribed to the vascular changes The plaquelike structures were well demonstrated by Mallory's phosphotungstic acid hematoxylin stain and consisted of a central, irregular granular body surrounded by a slight condensation of neuroglial fibers passing into the plaque Most of the plaques contained a few neuroglial fibers running radially through their outer part The plaques were most numerous in the cornu ammonis, the cerebellum and the inferior olive Many of the pyramidal neurons of the cornu ammonis had undergone Alzheimer's neurofibrillar change

The authors conclude that the vascular changes were not due to hyperpiesis and that the plaques were not the result of arteriolar degeneration but, rather, represented a metabolic dyscrasia of the central nervous system

FORSTER, Philadelphia

THE NEUROLOGICAL COMPLICATIONS OF DISSECTING AORTIC ANEURYSM AVERY D WEISMAN and RAYMOND D ADAMS, Brain **67** 69, 1944

Weisman and Adams reviewed 38 cases of dissecting aortic aneurysm and found in 11 instances neurologic signs bearing a definite relation to the observations at autopsy In these 11 cases the duration of illness lasted from six hours to nine days The cases were divisible into three groups on the basis of the pathologic process (*a*) ischemic neuropathy, 9 cases, (*b*) encephalopathy, 1 case, and (*c*) myelopathy, 1 case The neurologic complications were produced by interference with the blood supply of the peripheral or the central nervous system Clinically, in the cases of ischemic necrosis of the peripheral nerves the patients had pulseless, cold extremities, with weakness, anesthesia and areflexia In cases of ischemic necrosis of the spinal cord there appeared flaccid paralysis, urinary retention and a sensory level In a case of ischemic necrosis of the brain confusion, stupor or coma, with flaccid hemiplegia, hemianesthesia and aphasia prevailed In this case the aneurysm had occluded the left common carotid artery Dissecting aneurysm may occlude branches of the aorta in three ways (*a*) by extension of the dissection into the branch, (*b*) by thrombosis resulting from narrowing the lumen by dissecting aneurysm, or (*c*) by shearing of the small branches from the main trunk

FORSTER, Philadelphia

EXPERIMENTAL EDEMA OF THE BRAIN V VASCULAR PERMEABILITY S OBRADOR ALCALDE and J PI-SUÑER, Bol Lab de estud med y biol **1** 123 (July) 1942

Edema of the brain was again produced by lesions in the medulla in the region of the fourth ventricle Phenolsulfonphthalein was injected in large doses intravenously into animals Twenty to thirty minutes after injection the brain was removed and studied macroscopically In addition, emulsions of cerebral tissue were made, to which was added a 5 per cent solution of sodium bicarbonate, the emulsions were studied colorimetrically None of the coloring matter passed from the capillaries into the swollen cerebral tissue The dye did not pass into the cerebral substance even in those animals in which elimination of the dye into the urine was prevented In spite of this absence of experimental evidence in favor of an increase in vascular permeability in experimental edema of the brain, the authors showed in previous experiments that there is an increase in water content of the brain in these animals This fact would indicate the presence of some degree of capillary permeability The authors suggest that such permeability may be more readily demonstrable when the edema is of relatively longer duration It is also pointed out that histologic studies of these animals demonstrated as an almost constant finding the dilatation of perivascular spaces, indicating the probable existence of some degree of permeability

SAVITSKY, New York

Diseases of the Spinal Cord

TUMORS IN THE SPINAL CANAL IN CHILDHOOD II ANALYSIS OF THE LITERATURE OF A SUBSEQUENT DECADE (1933-1943), REPORT OF A CASE OF MENINGITIS DUE TO AN INTRAMEDULLARY EPIDERMOID COMMUNICATION WITH A DERMAL SINUS WALLACE B HAMBY, J Neuropath & Exper Neurol **3**·397 (Oct) 1944

Hamby states that in a survey of the literature in 1933 reports of 100 cases of intraspinal tumors in children of 15 years or younger were found In the subsequent decade (1933-1942, inclusive) 114 such cases were reported The distribution of neoplasms in the combined series was as follows gliomas, 20 6 per cent, sarcomas, 19 6 per cent, dermoids, 17 3 per cent, neurinomas, 10 7 per cent, lipomas, 4 7 per cent, meningiomas, 4 7 per cent, chloromas, 4 2 per cent, tumors

of blood vessels, 3 3 per cent, tumors of the sympathetic nervous system, 2 8 per cent, and miscellaneous tumors, 12 1 per cent In all, there were 21 "hourglass tumors," a percentage of 9 8 Seven cases of spinal epidural cysts are described in the literature of the last decade

Hamby reports the case of a 3½ year old boy who recovered from influenzal meningitis and a subsequent attack of meningitis Several surgical procedures were performed At first a sacral dermal mass was incised and drained Finally, an infected epidermoid cyst, extending from a sacral dermal sinus into the congenitally elongated spinal cord, was evacuated but could not be completely freed from the surrounding neural tissue

GUTTMAN, Philadelphia

THE CLINICAL SIGNIFICANCE OF BACTERIURIA IN PATIENTS WITH SPINAL-CORD INJURIES DANIEL BADAL, DONALD MUNRO and MARION E LAMB, New England J Med **230** 688 (June 8) 1944

Using the technic employed in the neurosurgical service of the Boston City Hospital, Badal, Munro and Lamb report their observations on cultures of urine of 53 of 169 patients with lesions at various levels of the spinal cord and cauda equina A total of 578 cultures were examined during the course of the study Proteus vulgaris, Escherichia coli, the alpha hemolytic streptococcus, enterococci and staphylococci were the most common organisms obtained from the patients with bacteriuria A group of 50 normal men served as controls

Asymptomatic bacteriuria may be present in a normal, active person without his knowledge and without the production of symptoms The presence of an indwelling urethral catheter is always accompanied with bacteriuria by the end of seventy-two hours, and patients who are treated with tidal drainage have an alkaline urine, which cannot be acidified Uncomplicated bacteriuria may be distinguished from infection of the urinary tract by the mode of onset of the latter, particularly when there is a sudden rise of body temperature, which is usually accompanied with a chill Also, observations on the clinical course and study of the patient's urine are of diagnostic value

The authors state that "sterilization of the urine in the presence of an indwelling catheter used as part of the tidal-drainage apparatus in treating patients with cord injuries has been impossible except by withdrawal of the catheter, and is unnecessary provided that the latest type apparatus is used and is properly adjusted to the bladder it is serving" Patients with injuries of the spinal cord who have infections of the urinary tract are best treated by properly adjusted tidal drainage, rest in bed and the administration of large amounts of fluid, preferably by mouth

Patients who recover from an injury of the spinal cord may have a normal genitourinary tract with normal function, without bacteriuria, unless they have had a transection of the spinal cord, a urinary calculus, a draining periurethral abscess or a lesion that has produced permanent physiologic or anatomic denervation of the bladder The patient with transection of the spinal cord may expect a reflex bladder without bacteriuria In ordinary circumstances there is no need for an indwelling catheter in this type of situation However, if there is denervation of the bladder as the result of injury, the bladder will be shrunken and useless, with subsequent bacteriuria and probably recurrent bouts of pyelitis

GUTTMAN, Philadelphia

PAIN AND DISABILITY OF SHOULDER AND ARM DUE TO HERNIATION OF THE NUCLEUS PULPOSUS OF CERVICAL INTERVERTEBRAL DISKS JOST J MICHELSEN and WILLIAM J MINTER, New England J Med **231** 279 (Aug 24) 1944

Michelsen and Minter report their observations on 8 patients who at the time of operation had a herniated nucleus pulposus in the lower cervical region There was a lesion at the fifth cervical interspace in 4 patients, at the sixth interspace in 3 patients and at the seventh in 1 patient, with involvement of the sixth, seventh and eighth cervical roots, respectively

The symptoms and signs were characterized by root pain and local sensory and motor disturbances, as well as by positive evidence in roentgenograms and on examination of the cerebrospinal fluid and injection of poppyseed oil The distribution of sensory abnormalities was compared with standard dermatome charts The sensory changes did not coincide precisely with those described in textbooks

The authors stress the importance of systematic neurologic examination of patients with pain or disability of the shoulder and arm in order to separate the apparently specific syndrome of cervical herniations of the nucleus pulposus from other entities due to extraspinal and from intraspinal lesions

Various so-called conservative methods of management had been tried for each patient, without permanent relief, prior to admission The laminectomy and removal of the fragment of disk produced good results in 6 patients In 1 patient the improvement was not impressive, while in another patient, 1 of the earlier ones, in whom the fragment of disk could not be removed for technical reasons, the pain was relieved but the motor disability persisted More recently the authors have performed subtotal hemilaminectomies, with good results

GUTTMAN, Philadelphia

Encephalography, Ventriculography, Roentgenography

THE ROLE OF X-RAY IN THE STUDY OF LOCAL ATROPHIC LESIONS OF THE BRAIN ARTHUR E CHILDE and WILDER PENFIELD, Am J Psychiat **101** 30 (July) 1944

Childe and Penfield reviewed the results of roentgenographic studies in 142 cases of focal epilepsy not due to expanding lesions The material included plain roentgenograms, cerebral pneumograms and cerebral arteriograms The authors found that unilateral atrophic lesions occurring early in life frequently produce cranial asymmetry, which can be detected in plain roentgenograms In cases of post-traumatic epilepsy frequently plain roentgenograms reveal no localizing information, but tears in the dura may result in destruction of bone through pressure of the brain and new bone formation Whenever focal cerebral atrophy is suspected, air encephalographic studies should be undertaken It is rare for an encephalogram to fail to demonstrate the location of the atrophic lesion Usually the exact site of a focal epileptic lesion cannot be demonstrated by air encephalography alone, and careful correlation of clinical, electroencephalographic and roentgenographic evidence is essential Occasionally cerebral arteriography is of value, especially when aneurysm or hemangioma is suspected

FORSTER, Philadelphia

ROENTGEN ANALYSIS OF UPPER CERVICAL SPINE INJURIES WALTER N PALMQUIST, Radiology **40** 49 (Jan) 1943

Palmquist describes a method for the precise interpretation of the roentgenograms of the upper cervical portion of the spine with the aid of index lines for guidance The first requisite of the method is a clear, accurate lateral exposure made with the patient in the erect posture For accurate analysis of the roentgenogram of the cervical region which does not demonstrate an obvious gross abnormality, at least six guide lines must be drawn In the presence of serious injury of the upper cervical region it may be possible to use only five lines Four lines will suffice when there is no injury of the upper cervical region and when normal hyperextension exists

The lines are drawn in the following manner 1 The first line is drawn in a horizontal plane passing medially through the body of the atlas and is designated as *a* 2 Three parallel lines are then drawn perpendicular to *a*, passing, respectively, through the point where *a* intersects the anterior surface of the upper odontoid process (line *c*), the point where *a* intersects the anterior surface of the tubercle of the atlas (line *at*) and the point where *a* intersects the mandible (line

am) 3 A fifth line *b* is drawn along the anterior edge of the body of the axis 4 A sixth line, *ab*, is drawn parallel to the vertical line *c* but passes through the lower anterior corner of the body of the axis The three guide lines parallel to the vertical line *c* determine three spaces, namely, *d*, *e* and *f*

It must be remembered that these lines are of significance only when the roentgenogram has been made with the subject in the erect position With the head in hyperextension their value is seriously impaired Spaces *d* and *e* are not appreciably affected by flexion or extension of the head

In the normal view the spaces *d* and *e* are equal, so that their ratio is 1 1 The line *c* will show the tubercle of the atlas to the left Test line *a* will be at right angles to test line *b*, which, in turn, will coincide with test line *c*, as does also the test line *ab*

Variations from the normal will readily demonstrate abnormalities not apparent on the roentgenograms unless the procedure outlined has been carried out

KENNEDY, U S N R

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

A J Arieff, M D, *in the Chair*

Regular Meeting, March 13, 1945

Progressive Hemiplegia Report of a Case Dr Joseph P Reich.

A man aged 60 noticed weakness in his left arm, which developed into almost complete hemiplegia within about four weeks Approximately two weeks later, after an attack of headache on the right side and convulsions involving his left arm, complete paralysis of the left leg and paralysis of the left lower portion of the face were found Eleven days later death occurred with the signs of acute respiratory paralysis During almost the whole course of the disease jacksonian attacks occurred several times a day, beginning in the left hand, at times limited to it and at other times spreading over the whole left side or even over both sides, with frequent deviations of the head and eyes to the left There was no loss of consciousness Slight haziness of the nasal borders of both disks was present but was not progressive The blood pressure and urine were normal The spinal fluid was normal, the pressure was not increased An air encephalogram, made two or three weeks after the onset of the first symptoms, showed nothing abnormal The anatomic diagnosis was tumor (glioblastoma multiforme) occurring principally in the white substance of the right hemisphere and extending into the adjacent precentral and postcentral gyri The anterior horn of the right lateral ventricle was compressed and shifted

The picture of "progressive hemiplegia" was first described by Oppenheim (*Internat Clin* **4**·177, 1899) and later by other authors The two pathologic changes most frequently associated with this condition were softening and tumor of the brain Mills and Spiller (*J Nerv & Ment Dis* **30** 385, 1900) reported a few cases, in which they noted slowly progressive degeneration of the pyramidal tracts

In the present case the diagnosis of tumor was made despite the absence of specific symptoms and of encephalographic evidence This diagnosis was based mainly on the frequent jacksonian attacks, which are rare with vascular lesions

DISCUSSION

Dr Paul C Bucy Dr Reich has presented an interesting and instructive case It is worth reporting, particularly because it illustrates some of the neurologic and diagnostic problems which have confronted neurologists so often in recent years A few years ago one saw most patients with cerebral tumor when the diagnosis was not difficult Today, however, patients come when the symptoms and signs are slight Therefore the neurologist has come to rely more and more on mechanical means of diagnosis, particularly on ventriculography and encephalography It is well, therefore, to realize that these methods are by no means free from error It is possible to have a tumor with an apparently normal subarachnoid space and ventricular system as demonstrated in the pneumoencephalogram, a situation I have encountered in several cases not unlike the one reported by Dr Reich

Dr George B Hassin In his discussion of the differential diagnosis, Dr Reich mentioned the progressive hemiplegia of Mills, which is a chronic disease process requiring years for its development, whereas the progressive hemiplegia in Dr Reich's case developed within a relatively short period I think the caption in Dr Reich's case should be "acute or subacute progressive hemiplegia" In

Mills's form the facial nerve is not involved, the paralysis is ascending, although it may also be descending, and the disease is evidently a form of amyotrophic lateral sclerosis Acute progressive hemiplegia may be due to vascular syphilis, instances of which I have reported (*Clin Rev* **20** 404, 1904, *Med Fortnightly* **23** 205, 1907) In such cases the process readily yields to antisyphilitic treatment.

Surgical Repair of Defects of the Skull Analysis of 120 Cases CAPT I JOSHUA SPEIGEL, Medical Corps, Army of the United States

I From an analysis of 113 cases of compound fracture of the skull initially treated overseas, with resultant defects of the skull, the following conclusions are reached

1 Adequate debridement performed as soon after the injury as possible, with closure of the wound in anatomic layers without drainage, is a highly dependable form of therapy for compound fractures of the skull
2 Free fascial transplants for dural defects, although in general useful, can be responsible for the maintenance of infection in a wound and should be used with that possibility in mind in any case of a potentially infected wound
3 The most frequent site of injury is the parietal region
4 The average size of the defect in the skull in this series was 5 cm
5 The neurologic sequelae frequently vary directly with the period of unconsciousness
6 The development of the "post-traumatic syndrome' of headache, dizziness and vomiting is inversely related to the severity of the injury

II The following technics in the repair of defects of the skull with tantalum have been tried and found useful

1 With screws
2 With wires
   (*a*) Through full thickness of the skull
   (*b*) Through partial thickness of the skull
3 With glazier's points
   (*a*) Without countersinking of the plate
      (1) Points through the plate
      (2) Points over the plate
   (*b*) With countersinking of the plate
4 With countersinking and "springing' of the plate into the defect

III The following technics in the preparation of tantalum plates have been tried and found useful

1 Hammering the plate over a concave and convex block
2 Bending the plate with curved dental forceps after slits are cut in the periphery of the plate
3 Accurate reproduction of the normal contours of the head with a die and counterdie

The last method is best if proper equipment and personnel are available

IV From an analysis of postoperative results in 120 cases of repair with insertion of a tantalum plate the following conclusions are reached

1 Serosanguineous fluid frequently forms over tantalum plates for a few days after the operation Aspiration of the fluid is without danger Its development can frequently be precluded by having numerous perforations in the plate and draining the operative wound for a few hours ofter operation

2 Any scars less than 3 mm thick and over 1 cm square which will lie over the tantalum plate should be resected, or they will break down

3 A musculocutaneous scalp flap is generally the best method of exposure, although frequently it is advisable to go through the old scar

4 If relaxing incisions must be made, they should not be in areas directly overlying the tantalum plate, as these areas will not fill in

5 In rare cases the tantalum will cause continual drainage of serosanguineous fluid and should be removed

6 After a period of four and a half months the plate is covered with a fine, smooth membrane, which is not adherent to anatomic structures or to scar

7 When infection exists, much time can be saved by excision of the infected area and closure (with relaxing incisions if necessary), followed in a few days by insertion of the plate Although the tantalum is a foreign body, its presence does not particularly encourage the onset of postoperative infection

8 Convulsive seizures can generally be precluded by the prophylactic administration of phenobarbital

9 In roughly 50 per cent of cases with minor neurologic sequelae, especially the "post-traumatic syndrome," the condition is greatly improved after insertion of a tantalum plate

10 In small series of cases "improvement" appeared in the electroencephalographic tracing after repair of the defect

11 In cold weather the tantalum plate becomes cold, with resultant slight discomfort

12 It is recommended that tantalum be available, in sterile condition, in all neurosurgical operations in which, for one reason or another, the sacrifice of a portion of the skull may become a necessity

DISCUSSION

DR A EARL WALKER Dr Speigel has presented an interesting paper which gives neurosurgeons many valuable hints on cranioplasty During and after each of the great wars there has always been an awakened interest in the repair of defects of the skull Many substances have been used for cranioplasty at various times In World War I an alloplastic material, pyroxylin, was favored In this war tantalum is widely employed One is struck by the fact that when tantalum is used for the repair of a large defect roentgenograms of the skull reveal little of the details beneath the plate In cases of such defects, which are usually associated with trauma to the brain and in about 40 per cent of which convulsive seizures develop, it seems desirable to be able to determine pneumoencephalographically the amount of distortion of the brain tissue In order to obviate this disadvantage of tantalum, methacrylate plates may be used These plates are not radiopaque, can readily be made in any shape and do not appear to produce any more tissue reaction than does tantalum For the larger cranial defects and those associated with damage to the brain, the use of a radiolucent plate has definite advantages For small defects probably tantalum is the best available substance

DR VICTOR E GONDA I understand that if tantalum stays in the body for longer than one or two years it becomes very fragile I should like to ask whether by putting holes in the plate there is any danger of the plate fracturing even more easily

CAPT I JOSHUA SPEIGEL, Medical Corps, Army of the United States I agree with Dr Walker that the presence of a large tantalum plate is a hindrance to accurate pneumoencephalographic study On the other hand, it is my impression that there will be fewer cases in which a convulsive disorder develops than there have in the past because of the more careful front line surgery, with accurate debridement and dural repair which is now available to the wounded soldier I agree, also, that a translucent material would be more desirable I have had no

experience with methacrylate plates, but Major Elkins, in another neurosurgical center, is using this material a great deal His results are apparently fully as good as are those with the use of tantalum I might mention, also, that in all our cases in which there is evidence of injury to the brain encephalographic and pneumoencephalographic studies are made before the plate is inserted

In answer to Dr Gonda, I cannot deny that putting holes in the tantalum plate weakens it somewhat, but I have never heard of a tantalum plate breaking, although I can conceive of its buckling if struck directly The statement that tantalum becomes fragile when it stays in the body for one or two years is news to me It is hard to believe that a substance as inert as tantalum can be changed by remaining in the body

Psychophysiologic Interrelationships DR MEYER SOLOMON

The term "psychophysiologic" seems preferable to "psychosomatic"

The terms "mentation" and "psychologic," "subjective" or "mental" activity seem preferable to "mind" or "psyche"

The activities within the psychophysiologic organism, or body, are divided into psychologic and physiologic, both of which are bodily, or organismal activities The physiologic bodily activities are divided into skeletal motor and skeletal sensory, visceral motor and visceral sensory and physicochemical (including hormonal)

The interrelationship between psychologic and physiologic functions may be (*a*) immediate (skeletal and visceral activities during running or fear), (*b*) remote (loss of weight from worry, insomnia or poor appetite), (*c*) direct, or primary, without any intermediate link (raising the arm under command) and (*d*) indirect, or secondary (suppurative, cardiovascular and other changes in simultaneous or antecedent, vigorous movements of the extremities and trunk)

Emotional activity is a combined psychophysiologic excitement, involving all levels and differing from vigorous voluntary activity in its psychologic state

Such psychologic activity as ideation, wishing and willing occurs in normal wakefulness, partial wakefulness of dreaming, simulation, hypnosis, hysteria and other psychoneuroses and psychoses

This discussion is concerned mainly with how psychologic can influence physiologic activity—how ideation (including wishing and willing) can influence skeletal motor, skeletal sensory, visceral motor, visceral sensory and physicochemical functions

The remote influence of psychologic on physiologic states is practically unlimited, through such factors as unhygienic habits, insomnia, anorexia and loss of weight

The immediate influence of the psychologic on each physiologic level was discussed separately

1 On the skeletal motor system
   (*a*) Ideas can immediately and directly lead to transient excitement and modification or suspension of function of the skeletal motor system
   (*b*) Ideas cannot lead immediately and directly to such disorders of a prolonged nature
   (*c*) Deep and superficial reflexes can be inhibited or exaggerated by skeletal muscular contraction
2 On the skeletal sensory system
   (*a*) Ideas cannot evoke, directly, transient or permanent sensory phenomena
   (*b*) Pain seems always to be of peripheral origin, centrally appreciated
   (*c*) Concentration of attention makes one more aware of normal or abnormal sensation from any area
   (*d*) Distraction of attention inhibits the degree of awareness of sensations
   (*e*) Ideas cannot produce continuous sensory loss

3 On the visceral motor system

1 Ideas can influence visceral muscles immediately and transiently, but only indirectly, the visceral manifestations being supportive, and secondary to or concurrent with primary activity of the skeletal motor system, as in voluntary activity or emotional response

2 There is an inhibiting or enhancing influence, directly and temporarily, on such partially voluntary activities as the functions of the urinary genital and respiratory systems and both ends of the digestive system

3 So-called voluntary control of the heart beat and the pupil seems no exception but is affected immediately, indirectly and transiently by momentary assumption of attitudes of tension, anxiety, expectation and fear

4 Even indirectly, ideas cannot produce permanent, prolonged or continuous changes in the visceral motor system

5 Ideation or suggestion cannot directly produce disorders of a vasomotor, secretory or trophic nature Conditioned salivary and gastric responses are but part of a total response of an excited organism

4 On the visceral sensory system

The same principles hold true for the visceral as for the skeletal sensory system

5 On the physicochemical, including the hormonal, system

These functions are not influenced directly, transiently or permanently by ideation but are part of emotional or voluntary activity

In general, ideas can lead immediately, but only indirectly, to transient functioning of the vegetative and physicochemical levels, by first producing activity of the skeletal motor system, which is accompanied with simultaneous adaptive changes in the vegetative and physicochemical systems, or by first exciting emotional response which involves all levels, including the skeletal

DISCUSSION

DR CHESTER DARROW Dr Solomon has raised many controversial questions Owing to the lateness of the hour, I may discuss only a few

Like Dr Solomon, I, too, feel more comfortable with the term "psychophysiologic" than with the term "psychosomatic," but I can find little quarrel with those who like the latter term It is not something new The term "psychosomatic" and a discussion of the problems implied were recently called to my attention in a Mid-Victorian novel, "Hard Cash," written by Charles Reade in 1868

One may question Dr Solomon's definition of the field of psychology as the study of "subjective and conscious processes" There surely would be a protest from psychologists should one thus "fence it in" Psychology is concerned not merely with the conscious and the subjective but also with those adaptive functions of the nervous system which permit modification of behavior by experience This is true of the skeletal system, and secondarily also of the autonomic system Such learning and retentive functions are not necessarily either subjective or conscious, but they are functions of the mind I suspect that it is by means of learned sequences of response—neuronal, skeletal and autonomic—that many psychophysiologic effects are accounted for

I heartily approve Dr Solomon's differentiations of psychophysiologic relationships into immediate and remote, direct, or primary, and indirect, or secondary Recognition of such differences may prevent much loose thinking It should, however, be emphasized, and Dr Solomon will doubtless assent, that directness is largely a matter of degree Most psychophysiologic effects, as he himself emphasizes in the case of posturally induced autonomic changes, are indirect It may be questioned whether even postural events are not likewise secondarily induced, if one carries the analysis far enough

Indeed, it is present day recognition of the indirectness of control, together with recent advances in knowledge of neurology, humoral transmission, glandular secretion, function of moderator nerves and metabolic processes, that has contributed as much as anything to the discarding from psychiatry of symbolic magic and to the abolishment of witch doctor technics It has permitted the tracing of neurophysiologic dynamic mechanisms, which formerly were a sealed mystery Sequences by which spastic colon, gastric ulcer or hypertension may derive from ideas or attitudes become clearer, and better methods of control are acquired

An indirect mechanism which my associates and I sometimes see in our own laboratory is that of fits or seizures which are suspected of having a hysterical basis but which on examination appear to be precipitated either deliberately, by voluntary hyperventilation, or unintentionally, as a result of emotionally induced hyperventilation

Certainly, I should agree that emotion may begin in the brain A man's blood pressure can be shown to rise at the sound of a certain word In his extracurricular education he presumably learned the meaning of that word, and his present recognition of the meaning implies cerebral activity I do not, however, accept the statement that reverberations from the periphery or from the basal ganglia never initiate, or even augment, emotion On the contrary, psychologic and psychiatric observation and physiologic experiment support the view that they may How often is there indication to the psychiatrist of an unfixed, generalized, "free-floating" anxiety, tension, hostility or depression, existing, as it were, in supersaturation and ready to crystallize about the first psychologically sufficient impurity in the preceptual field! In such cases the emotion seems to lurk in the physiologic mechanism, while the brain merely provides an acceptable direction for its escape or, in some cases, merely rationalizes the event post facto

As to the statement that ideas do not modify preception I think the experimental work cited by Dr Wallenberg at a recent meeting of this society should go far toward refuting such a view The question appears to me particularly important at the moment because of indications from studies by my associates and myself that autonomic function and emotion may modify the electroencephalogram Such evidence for neurophysiologic "feed-back' to the brain during ideation and emotion seems to offer one more neurophysiologic mechanism to account for psychophysiologic effects of the type which Dr Solomon has discussed

DR MEYER SOLOMON I appreciate Dr Darrow s fine discussion There is considerable difficulty in the use of terms, which are often not clearly defined I have tried, perhaps unsuccessfully, to define in what sense I have used the various terms The sequence of events is important I did not mean to be dogmatic, rather I wished to point out some problems for research in the field of psychophysiologic interrelations One must carefully differentiate between mentation, or psychologic activity, and emotional activity, which is psychophysiologic It seems to me that the whole field of psychophysiologic, or so-called psychosomatic, interrelationships needs careful, critical review, with emphasis on relationships or influences which are immediate or remote, direct or indirect

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NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Combined Meeting, March 13, 1945

Byron Stookey, M D, *President, New York Neurological Society, in the Chair*

Ménière's Syndrome Comparison of the Results of Medical and Surgical Treatment DR MILES ATKINSON

This paper was published in full in the September 1945 issue of the ARCHIVES, page 192

DISCUSSION

DR BRONSON SANDS RAY Dr Atkinson has asked me to present results of the surgical treatment of Meniere's syndrome Various surgical procedures have been, and are still, employed, but the one which I believe to be most useful and with which I have had experience is division of the eighth nerve intracranially This operation has been employed by neurosurgeons for the past fifteen years My conclusions are based on personal experience with 40 patients subjected to section of the eighth nerve during the last seven years During this period I have seen a great many other patients who had more or less definite symptoms of Menière's syndrome, and I have advised operation perhaps for as many patients as I have operated on It is important to adhere to the three criteria necessary for diagnosis of Meniere's syndrome paroxysmal vertigo, tinnitus, and progressive loss of hearing on the side of the tinnitus when the latter is unilateral

An analysis of the cases has brought out some interesting points The age incidence was between 20 and 70, 15 per cent of the total number of patients were in each of the third, sixth and seventh decades of life In the fourth and fifth decades the incidence was higher, namely, 25 and 30 per cent, respectively The distribution was about equal between the two sexes In 25 per cent the first symptom to appear was an attack of vertigo, in 32 per cent, unilateral tinnitus, and in 30 per cent, impairment of hearing In 4 per cent two or more of these symptoms occurred simultaneously in the beginning In 6 patients the condition might be classified as bilateral, since there were tinnitus and impaired hearing on both sides, but in each patient the hearing defect and the degree of tinnitus were greater on one side All patients had some impairment in hearing Ninety-two per cent of the patients had lost 35 per cent or more of their hearing on one side; none was totally deaf on even one side Caloric tests showed normal responses in 32 per cent, absence of vestibular response in 12 per cent, impairment of vestibular response in 36 per cent and an increase of the normal response in 20 per cent—all on the side of the tinnitus and loss of hearing when these were unilateral. Various combinations occurred in the patients with bilateral tinnitus and loss of hearing Seventy-five per cent of the patients had been under some form of medical therapy, without sufficient benefit, prior to operation Some of these patients had been treated by Dr Atkinson medically, and he believed they had not responded adequately

In 40 per cent of the patients a total division of the eighth nerve was performed, in 60 per cent, only a partial division, i e, a section designed to interrupt the vestibular part of the nerve and to preserve as much as possible of the acoustic portion There was 1 postoperative death, that of a patient with hypertension who died suddenly of a cerebral vascular accident In 2 patients the attacks of vertigo were not abolished In both these patients partial division of the nerve had been done, and caloric tests made postoperatively showed that some of the vestibular portion of the nerve remained functional in both On 1 of these 2 patients a second operation was done, and total section of the nerve completely relieved the attacks The other patient did not wish to have a second operation Thus, with these 2 exceptions, every patient was relieved completely of attacks of vertigo

The effect of the operation on tinnitus was somewhat variable In general total section of the nerve was more advantageous, for 50 per cent of the patients having total section were completely relieved of tinnitus, whereas only 15 per cent of those with partial division had complete relief In about one-half the patients there was some degree of unsteadiness for a matter of several weeks to months after operation This was most noticeable to them on sudden change of position, but all eventually found that the symptom disappeared completely or became so slight that it was unimportant to them Interestingly, a number of patients claimed that their everyday hearing was improved even when total section of the involved nerve was performed

In the group with bilateral tinnitus and impaired hearing the results were gratifying I was led to believe from others' experience that in cases of bilateral

Meniere's syndrome bilateral section of the nerve was sometimes necessary, but I have not found this to be true Dr Atkinson has suggested that the patient with one eighth nerve destroyed will not experience vertigo, since the occurrence of vertigo may somehow be dependent on the imbalance between two intact mechanisms Of course, in the patients with bilateral impairment of hearing it is perhaps more important to perform a partial section of the nerve, in an attempt to preserve all the residual hearing that the patient has

Except for transient postoperative weakness of the face in 2 cases, there were no untoward complications of the operation In general it may be said that the operation is a satisfactory one, for if all the vestibular portion of the nerve is divided abolition of the paroxysms of vertigo can almost be guaranteed In the majority of cases I have come, rather, to prefer total to partial section of the nerve This attitude is due to the fact that only a few patients have much useful hearing in the involved ear at the time they come for operation, to the better chance of terminating the tinnitus with total division of the nerve and, finally, to the possibility that the attempted preservation of the acoustic portion of the nerve may result in incomplete section of all the vestibular fibers It is true that the operation entails craniotomy and is potentially hazardous, but the complications should be few and the mortality low Most patients are up and about in a few days and require about ten days' hospitalization For selected patients I consider the operation eminently satisfactory

DR MILES ATKINSON I agree with Dr Ray that the patients must be carefully selected and that one may expect success in 100 per cent of such cases Dr Ray's point that bilateral nerve section is not necessary in cases of bilateral Meniere's disease is of great importance I think Dr Ray, you said you had never had to do such an operation?

DR BRONSON SANDS RAY That is correct

DR MILES ATKINSON I am quite sure it is a bad thing to do It is never necessary in cases in which the diagnosis has been correctly made and should not be performed at all in cases in which the diagnosis is incorrect

DR LEON H CORNWALL Dr Ray said that the mortality rate for these operations should be low but he reported 1 death in his series of 40 cases That is a mortality rate of 2 5 per cent Does he regard that as low?

DR BYRON STOOKEY May I answer Dr Cornwall's comment by saying that I consider it extremely low? The operation is a serious one, and a suboccipital decompression is done I think Dr Ray's results are excellent In my opinion, total resection of the eighth nerve is far superior to a differential section

DR BRONSON SANDS RAY The rate is a relative matter, 2 5 per cent is a comparatively low mortality rate, but though it might be lower in a larger series of cases one is never justified in disregarding the hazard of any operation

Relation of Nerve Impulse to Metabolic Processes DR R LORENTE DE NO (by invitation)

Clinical Diagnosis of Disturbances of the Central Sympathetic System by Means of Pupillography DR OTTO LOEWENSTEIN

As far back as 1908, Eppinger and Hess created the conception of sympathicotonia and vagotonia, by which, for the first time, a clinical approach to the diagnosis of diseases of the autonomic nervous system became possible Subsequent clinical observations, however, showed that their conception was either not quite correct or incomplete The work done subsequently by physiologists, particularly Langley, Sherrington, Starling, Gaskell, Bayliss, Elliott, Cannon and Bard, and by pharmacologists, particularly Hans Horst Meyer, Otto Loewi H H Dale and their followers, created the basis for a better understanding of the clinical observations on the autonomous nervous system

Nevertheless, one is still far from being able to examine the sympathetic nervous system clinically, in particular, the differential diagnosis of central and peripheral disturbances is frequently difficult or even impossible

In order to show the importance of pupillography for this clinical purpose, I wish to start with a physiologic statement The parasympathetic system discharges in the form of local reflexes, that means that only one outflow, or only a part of one outflow, is active at a time The sympathetic system, however, tends to discharge *en masse* For instance, when light is thrown into the eye, the only visible effect is contraction of the pupil, however, when I touch the eye, causing pain, there results not only dilation of the pupil but a total sympathetic discharge The latter includes vasoconstriction of the blood vessels in the viscera and skin, elevation of the eyelid, and therefore widening of the palpebral fissure, acceleration of the heart rate, and increase in blood pressure All organs provided for by the sympathetic nervous system are included, all effects are the immediate expression of the same stimulation, extending all over the body and controlled by the center

In view of the discharge *en masse* and the radiation of sympathetic outflows over the body, every organ which is innervated by both the sympathetic and the parasympathetic system may become a test object for the mechanisms of autonomic control

The pupil, especially, is suited to such analysis, for the following reasons First, the iris is immediately visible, second, a great number of sympathetic and parasympathetic reflexes may be easily elicited in the pupils, and, third, the method of pupillography enables one to make an analysis of pupillary movements in every desirable degree of precision

By recording the effects of stimulation of the hypothalamus, one could show that the posterior and lateral hypothalamic nuclei are chiefly concerned with sympathetic discharges, while the parasympathetic mechanism may be localized in the nuclei of the anterior portion and the midline, in the region of the tuber cinereum Representation of pupillary activity, in both its sympathetic and its parasympathetic division, in the hypothalamus, where so many vegetative centers are distributed over a relatively small area, explains why analysis of pupillary function is so important No extensive pathologic process, either irritative or destructive, is conceivable without participation of the pupillary hypothalamic pathways or centers, either as direct or as neighborhood signs

The clinical syndromes concerned are diabetes insipidus, emaciation, adiposogenital dystrophy, hyperthermia, hypersomnia, epilepsy of autonomic origin and personality changes, particularly psychoneuroses

It appears from pupillographic studies that some pathologic pupillary reactions are combined with some hypothalamic symptoms more frequently than with other hypothalamic symptoms A certain number of pupillary reflexes are considered to be predominantly, although not exclusively, parasympathetic reflexes, such as the blinking reflex, the reflex to near vision and the reflex to light Other reflexes are considered to be predominantly sympathetic reflexes, such as the reflex to darkness, the reflex to sensory and psychologic stimuli, the corneal and conjunctival reflexes and the psychosensory restitution phenomenon, of which I shall speak later

All these reflexes undergo certain modifications characteristic of the site of the lesion Absence or diminution of the psychosensory dilation phenomenon is characteristic of a lesion in the second or third sympathetic neuron, i e, peripheral to the center of Budge, it is definitely located in the third neuron when cocaine no longer dilates the pupil while epinephrine dilates it

When the pupil contracts to light and does not dilate again, one is concerned with a "sympathetic block," which may be partial or complete The sympathetic block is a central inhibition phenomenon, indicating a disturbance in the central sympathetic system

When the light reflex of the pupil is elicited again and again, fifty to one hundred times or more at intervals of four seconds the latent period becomes longer and longer a refractory period develops, and the contraction becomes increasingly sluggish and inextensive When the refractory period becomes longer

than the interval between application of the light stimuli, the pupil no longer reacts to light, i e, it has become exhausted for the particular period of stimulation employed When, nevertheless, stimulation of the pupil at the same interval is continued, with, however, a psychologic or sensory stimulus interposed between two light stimuli, the pupil, which up to then was exhausted, reacts again to the subsequent light stimulus (psychosensory restitution phenomenon, Lowenstein) Absence of the psychosensory restitution phenomenon points to a central lesion, exaggeration, to a central irritative condition

The contraction to light consists of three phases—the primary, secondary and tertiary contraction phases In a case of cyclic sympathetic paralysis (Lowenstein, O, and Levine, A S Pupillographic Studies V Periodic Sympathetic Spasm and Relaxation and Role of Sympathetic Nervous System in Pupillary Innervation, ARCH OPHTH **31** 74 [Jan] 1944) and cyclic oculomotor paralysis (Lowenstein, O, and Givner, I Cyclic Oculomotor Paralysis, ARCH OPHTH **28** 821 [Nov] 1942) it could be shown by means of a well elaborated timing system that the primary contraction phase is predominantly due to parasympathetic factors, whereas the secondary and tertiary contraction phases are predominantly due to sympathetic factors Absence or underdevelopment of the second contraction phase points to a lesion which is predominantly, if not exclusively, of the central sympathetic system

Cases exist in which not only within the contraction phase of the pupillary reflex to light but in the redilation phase the parts conditioned by the central sympathetic system seem to be cut off, this leads to a type of reaction which I described, in collaboration with Westphal, for the first time in 1933 and which was named tonohaptic reaction

Finally, I wish to mention two other types of reaction to light which are due to central sympathetic conditions 1 The so-called climbing pupil This type is characterized by the fact that the redilation is more extensive than the preceding contraction, causing the pupil to become larger after subsequent stimulations with light 2 The so-called cogwheel reaction, in which both contraction and dilation occur in steps These steps are due to sympathetic inhibitory influences

A certain affinity exists between the various types of pupillary symptoms described and the various clinical diencephalic syndromes, particularly those of the hypothalamus, some pulpillary symptoms are always combined with clinical symptoms, while others are frequently combined A certain group of pupillary symptoms of undoubtedly sympathetic origin seems to occur independently, that is, they are not combined with other symptoms of known hypothalamic origin but are linked with psychologic symptoms and occur under the guise of a psychoneurosis Sometimes they may precede the occurrence of clinical symptoms In cases of postencephalitic hypersomnia, for instance, we observed the tonohaptic type almost exclusively, and the same is true of catatonia, in cases of hyperthermia we observed exclusively the climbing pupil, and in a certain group of cases of hyperthyroidism, those in which exophthalmos was a complication, we observed almost exclusively the sympathetic block Absence of the psychosensory restitution phenomenon combined with the tonohaptic reaction occurs exclusively with chronic conditions Those pupillary phenomena which are always linked with certain other clinical hypothalamic symptoms are likely to be due to the direct involvement of pupillary centers or pathways in the same pathologic process, those phenomena which are frequently linked with them probably must be considered as neighborhood symptoms In more than 80 per cent of cases psychoneurotic symptoms are combined with central sympathetic (or parasympathetic) pupillary phenomena, here too, it appears that certain psychologic unities are always and exclusively combined with certain pupillographic types

DISCUSSION

DR ISADORE GIVNER Dr Lowenstein has asked me to comment on the importance of pupillography in ophthalmology I have had the opportunity of working with him on three problems, first, glaucoma second, retinal angiospasm and, third, the exophthalmos of hyperthyroidism With regard to glaucoma For

a long time we have felt that a central factor is involved in the control of intraocular tension Dr Lowenstein has been able to show for the first time that in patients with chronic simple glaucoma there is a disturbed pupillographic pattern in the unaffected eye, indicating that these persons have the conditions for the development of glaucoma in the opposite eye as well With regard to retinal angiospasm We studied several cases in which there was a central sympathetic factor Also, we have studied 22 cases of exophthalmic goiter with the pupillographic method In 21 of the 22 cases there was a definite pattern, which, as Dr Lowenstein interprets it, was a central sympathetic pattern

Pupillograms are made at a speed of 100 pictures per second A normal tracing shows a latent period followed by a contraction and a latent period followed by redilation In cases of hyperthyroidism there is a redilation block So constant has been this observation that it occurred to me that the pattern might be of value in doubtful cases with unilateral exophthalmos I should like to show kodachromes in 2 cases

CASE 1—In a case of unilateral exophthalmos, a roentgenogram of the skull made elsewhere was reported to show nothing abnormal The pupillographic tracings were normal In order to check on the roentgenographic studies in this case, a stereoscopic roentgenogram was taken, it showed a meningioma of the sphenoid ridge

CASE 2—A nurse with unilateral exophthalmos had a basal metabolic rate of +4 per cent With a 100 mm base line, the exophthalmometric measurements were 20 mm for the right eye and 18 mm for the left eye The palpebral aperture was wider on the right side The pupillographic tracings showed a typical redilation block We felt, therefore, that her exophthalmos was based on dysfunction of the thyroid

Dr Lowenstein is to be congratulated on giving this additional laboratory aid in the diagnosis of disorders of the central sympathetic system

DR OTTO LOWENSTEIN This paper was concerned with pupillographic features of lesions of the sympathetic system, either central or peripheral, and their differential diagnosis for clinical purposes It was not concerned with lesions of the parasympathetic system From pupillographic and clinical, as well as from purely clinical, evidence, sympathetic and parasympathetic disturbances appear to be interdependent, and only consideration of the whole picture enables one to make a diagnosis

Protest A Recorded Psychiatric Program MAJOR ALBERT A ROSNER, Medical Corps, Army of the United States

A sound reel of a psychotherapeutic session with soldiers was presented

Book Reviews

The Psychology of Seeing By Herman F Brandt, Ph D Price, $3 75 Pp 240 New York Philosophical Library, 1945

This book is a compilation of studies done at the Visual Research Laboratories of Drake University, Des Moines, Iowa The general areas of research are "Instrumentation for Objective Observation', 'Basic Eye Movements", "Advertising—Evaluated by Photography", "Learning—Revealed by Ocular Performance", "Art—Judged by the Response of the Observer", "Ocular Patterns," and "Psychological Implications" These sections are preceded by an introductory chapter and are followed by a section on projected studies, a brief bibliography and a glossary The general approach is toward the layman, on the assumption that he understands little about vision

Among the new equipment described, there is a portable bidimensional camera which records every movement of the subject s eyes and the fixation of his eyes while reading The author also reports a series of tests for determining the preferred positions in ocular movements Through utilization of the method of ocular photography, several technics have been elaborated to determine the efficacy of various advertising devices The author has investigated the attensity of isolation and concludes that the use of white space for creating the state of isolation in an advertisement has not been fully appreciated and should be more regularly employed With regard to color, the results show that red had no attentional advantage over black and white, except when utilized in headline form

The author has been ingenious in applying the method of ocular photography to a variety of advertising problems, such as the determination of what relative amounts of time are devoted by men to the different parts of a woman's body, and likewise by women to the different parts of a man s body The upper half of the man's body is dominant in attention-getting value, especially the face, collar and tie For the woman, however, the foci of maximal attention are the hair, eyes and mouth This was determined under the condition of asking the men to judge the age of a woman, whereas the women were asked simply to look at a man The implications of this difference are obvious, especially in view of the absence of any emphasis on the woman's legs and feet

Dr Brandt has devised a series of designs in order to compare horizontal and vertical ocular movements and suggests that ocular photography will play an increasingly larger role in evaluating visual learning On the basis of several experiments, the author makes some concrete teaching suggestions for improving instruction in algebra, arithmetic, spelling and geography

Without entering into the nature-nurture controversy with regard to intelligence, Dr Brandt contends that much about the intelligence of a person may be discovered by the study of his ocular performance It is, of course, well known that perceptual acuity plays a great role in general intelligence and one's ability to learn, retain and reason What seems more essential to the reviewer, however, is that motivational and emotional factors may influence perceptual acuity

Toward the latter part of the book are discussed the applications of ocular photography (ophthalmography) to reading diagnosis remedial therapy for reading difficulties, a study of how children read pictures and copy and the judgment of art as determined by ocular fixations

After listing the essential determinants of attention and briefly discussing the problem of individual differences, Dr Brandt closes the book with a consideration of some of the problems which have yet to be studied through ocular photography Among these are certain unsolved problems in optometry, illumination and lie

detection, the general problem of efficiency, the relative importance of peripheral and foveal vision in relation to specific aptitudes for certain skills, and the importance of ocular movements as an additional evidence of alcoholic intoxication

Dr Brandt has succeeded in broadening the range of applicability of the technic of ocular photography from its originally narrowed use as a test in reading diagnosis While there is less likelihood of any important theoretic discoveries emerging from the use of the technics developed, this book certainly illustrates the importance of evaluating ocular movements in a large variety of practical problems and is replete with many experimental suggestions

O tratamento cirurgico das doencas mentais By M Almeida Amaral, M D, with a preface by Egas Moniz Price not given Pp xv, plus 149, with 18 illustrations Lisbon, Portugal Livraria Luso-Espanhola, 1945

A further report on psychosurgery has long been awaited from Portugal, where this procedure was first developed The present volume, however, is a distinct disappointment It details only a dozen cases, in some of which the patient was followed for only a brief period, although recoveries of seven and eight years are described in the case reports The arguments in relation to mechanism are presented in incomplete fashion, and a good deal of the book consists in a rehashing of observations and opinions already found in the literature The bibliography is incomplete and contains numerous errors The preface by Egas Moniz deals largely with the theories of Pavlov and their application to psychiatry, particularly as related to breaking up of the anatomic mechanisms underlying conditioned responses through prefrontal leukotomy The author admits that, unfortunately, it has been impossible in Portugal to apply the operation on a large scale to sufferers from mental disorder Of his 12 patients, 6 recovered, 3 improved, the condition of 2 was unchanged and 1 died

The Person in the Body By Leland E Hinsie, M D Price, $2 75 Pp 264 New York W W Norton & Company, Inc

With the aid of much illustrative material from case histories, the author describes the forces which operate in the production of psychosomatic disturbances He uses freudian principles and labels in identifying these forces and in tracing them to their origins He does not, however, include the more labyrinthine interpretations but indicates, rather, that much change can often be effected by relatively simple psychotherapy

The book is written for the physician who has had no special training in psychiatry and for the layman who might come to him for a psychosomatic complaint In general, the book follows the growth of the person and points out the corresponding relationships of body and mind in the process and how often body and mind have to play "under-study" roles for one another The mass of clinical data cited will carry conviction of the reality of the problem to the practitioner, who is likely to be the first to meet with cases of these disorders There is a short chapter on the principles of psychotherapy

The book is recommended

Aviation Neuro-Psychiatry By R N Ironside, M B (Aberd), F R C P (Lond), and I R C Batchelor, M B (Edin) Price, $3 Pp 168 Baltimore The Williams and Wilkins Company, 1945

The authors have written a practical guide to aviation neuropsychiatry The studies are essentially descriptive, and no attempt is made to study the disorders dynamically, as has been done by other writers Although the cases cited are based on wartime experiences, the authors are apparently oriented toward the needs of a peacetime aviation Qualitative rather than quantitative considerations will guide the selection authorities of the future With this in mind, the authors

stress the importance of a thorough psychiatric examination of prospective flying personnel They minimize categorically the importance of special aptitude tests and also disagree with those who believe that the only test for combat is combat In point, they state, "The temperamentally unstable in the affairs of everyday life are unlikely to become temperamentally stable by leaving the ground and becoming aviators"

With a thorough understanding of aviation physiology the psychiatrist will be better able to evaluate hysterical and neurotic symptomatology Aviation physiology is briefly but clearly discussed in this book

There is certainly a justification for a book of this sort, but it can be used only as a guide, rather than as an exhaustive treatise on the subject The authors make no claims which they do not clearly fulfil The beginner in aviation psychiatry will do well to use this as an introductory guide

Hypnoanalysis By Lewis R Wolberg, M D, Price, $4 Pp 342 New York Grune & Stratton, Inc, 1945

In this book the author discusses hypnoanalysis, chiefly on the basis of material in the case of Johan R He presents sufficient detail to make clear to the reader the facts from which are derived therapeutic technics and procedures used In recent years one has witnessed the salutary appearance of books dealing with psychotherapy in which case reports are described This makes it possible for the reader to evaluate the material and results in a much more definite manner The patient, Johan R, chosen by Dr Wolberg, has the capacity for expressing himself so well that it makes the reading of the case material of more interest than is usual in scientific reports

There is recorded rather well the integrative use of hypnosis and analytic therapy Apparently, it was possible by hypnoanalysis to make rapid strides in the treatment of a patient who was severely ill At least in the case of this patient the procedure was a short cut to the desired end result Without the use of hypnosis the analytic procedures either could not have been used or would have resulted in a much more prolonged therapy

Numerous technics are used to facilitate the recapture of buried memories and to facilitate insight The author uses hypnotic regression, hypnotic induction of dreams, hypnotic induction of phobias, hypnotic suggestions, automatic writing and the crystall ball induction of hallucinatory experience These procedures and their role in therapy are ably described

It is well to remember, as Dr Wolberg points out, that the discovery of buried memories during hypnosis and their immediate use for therapy in the conscious state will often fail to be of benefit Frequently the implications that these memories impart will not be accepted by the patient in the conscious state until he himself realizes their importance and presents the interpretation as a product of his own efforts and conviction An effective technic to achieve this result is to instruct the patient under hypnosis to forget what he has learned until he is convinced of the truth of his memories and understands them thoroughly Another technic is to revivify these memories by inducing the patient, under hypnosis, to see the recalled scenes in a crystal ball or mirror This usually induces such profound emotional reactions that the patient's acceptance of them is greatly facilitated

There is a good discussion of the relation of hypnosis and the transference situation, how the various resistances are to be manipulated and in what manner analytic interpretation is utilized in hypnoanalysis

This book is a worth while contribution to the field of psychiatric therapy It should be read by all workers in this field

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