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CONTENTS OF PREVIOUS NUMBER

JULY, 1932. NUMBER 1

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VOLUME 28 AUGUST, 1932 NUMBER 2

CORTICONUCLEAR TRACTS FOR ASSOCIATED OCULAR MOVEMENTS

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PHILADELPHIA

The associated movements of the eyeballs have interested me [1] for many years, especially since my presidential address before the American Neurological Association in 1905. It is my purpose now to discuss the corticonuclear tracts for associated ocular movements, but one is dismayed in beginning this undertaking by the paucity of accurate knowledge. No one doubts that these movements are represented in the cerebral cortex, and information regarding this representation for lateral movements is fairly satisfactory. Gordon Holmes [2] stated that the movements of the head and eyes by electrical excitation were originally described by Ferrier, but the zone from which they can be evoked is relatively a very small part of the frontal cortex.

Foerster [3] has confirmed the existence of a center for lateral ocular movements also in the posterior part of the superior temporal convolution, and its borders are not well defined. Stimulation here produces adversive movements similar to those obtained from the frontal adversive field, which occupies the posterior part of the superior frontal convolution—rotation of the head, eyes and trunk to the opposite side.

Read at the Fifty-Eighth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1932.

1. (*a*) Spiller and Potts: Pathological Report and Remarks on Palsy of Associated Ocular Movements, Univ. Pennsylvania M. Bull. **16**:362, 1903. (*b*) Spiller, W. G.: The Importance in Clinical Diagnosis of Paralysis of Associated Movements of the Eyeballs (Blicklähmung), Especially of Associated Movements, Upward and Downward, J. Nerv. & Ment. Dis. **32**:417 and 497, 1905; (*c*) Paralysis of Upward Associated Ocular Movements, Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **15**:352, 1907; (*d*) Bilateral Oculomotorius Palsy from Softening in Each Oculomotorius Nucleus, Névraxe **14**:125, 1913; J. Nerv. & Ment. Dis. **40**:792, 1913; (*e*) Ophthalmoplegia Internuclearis Anterior: A Case with Necropsy, Brain **47**:345, 1924; (*f*) Remarks on Oculogyration and on the Lesion Causing Complete Bilateral Ophthalmoplegia, Am. J. M. Sc. **157**:695, 1919; (*g*) Unilateral (Unassociated) Innervation of the Ocular Muscles, Arch. Neurol. & Psychiat. **18**:691 (Nov.) 1927.

2. Holmes, G., and others: The Mental Symptoms Associated with Cerebral Tumors, Proc. Roy. Soc. Med. (Sect. Neurol. & Psychiat.) **24**:65, 1931.

3. Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309 (Aug. 8) 1931.

The cortical representation for vertical associated ocular movements has largely eluded detection. Edwin Bramwell,[4] in his presidential address before the Neurological Section of the Royal Society of Medicine, on Oct. 13, 1927, stated that observers who have studied the effects of stimulation of the cortex in normal animals and in man have failed to produce an upward or downward movement of the eyes. He quoted Hughlings Jackson's opinion that the lateral movements of the eyes might be so much more powerfully represented in the cortex than any of the other ocular movements that they overpower the latter when the eye area is stimulated. Risien Russell stimulated the eye area of the cerebral cortex on one side after previously dividing the internal rectus of the eye on the same side and the external rectus of the eye on the opposite side and found that he was then able to elicit upward and downward movements of the eyeballs, and from this experiment he concluded that Hughlings Jackson's explanation was correct.

An excellent critical digest of the literature of associated ocular movements has recently been written by Riley.[5] He speaks of control of ocular impulses descending from suprasegmental sources, meaning from the cerebrum, and also of suprasegmental lesions, and said that suprasegmental lesions may produce loss of lateral deviation without the nuclei or centers of lateral movement being involved. This opinion, held by Riley, possibly is true only of transitory paralysis unless the tracts from both sides of the brain are involved, for conjugate deviation of the eyeballs is common in the onset of an apoplectic stroke, but is of comparatively brief duration. Riley said that the loss of conjugate vertical gaze has been associated by many authors with lesions in the vicinity of the collicular plate, and neoplasms of the epiphysis almost regularly show this disturbance in movements of the eyes. Sufficient clinical evidence supported by autopsy observations in his opinion has accumulated to warrant the assumption that the superior colliculi control the vertical movements of the eyeballs, either through the presence of a center or through fiber pathways that pass through the colliculi.

In contrast with this view, Dejerine [6] believed that the lesion that produces the syndrome of Parinaud is situated in the region of the anterior quadrigeminal tubercles, and in support of this statement he referred to the fact that I found these structures affected in nineteen of twenty cases; but in addition to this lesion there is also a lesion of the subthalamic aberrant fibers of the peduncular path. In my paper, in 1905, I distinctly expressed the opinion that paralysis of vertical

4. Bramwell, Edwin: The Upward Movement of the Eyes, Brain **51**:1, 1928.

5. Riley, H. A.: The Central Nervous System Control of the Ocular Movements and the Disturbance of This Mechanism, Arch. Ophth. **4**:640 (Nov.); 885 (Dec.) 1930.

6. Dejerine, J. J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1914, p. 1139.

gaze does not depend on lesions of the superior colliculi of the corpora quadrigemina, and although I referred to a considerable number of cases in which these structures were implicated, I also referred to other cases in which they were intact. There is no evidence, in my opinion, that justifies the assumption of a supranuclear center in the superior colliculi. A lesion involving them is one that is close to the oculomotorius nuclei or one that is likely to interfere with the corticonuclear paths. There is no lesion of the superior colliculi in my case recorded in the present paper, or in the cases of Lhermitte and Kraus, Collier or Dereux. In my paper of 1905, I cited cases in which the corpora quadrigemina had been destroyed without disturbance in the movements of the eyeballs.

The paper by Schaeffer and Blum [7] is a good presentation of the problems involved in paralysis of vertical gaze, but it contains no new material and no cases of their own, and is confined to paralysis of vertical gaze.

The following case was seen in the service of Dr. Alfred Stengel at the University Hospital, and I report it with the permission of Dr. Stengel.

REPORT OF CASE

History.—McD., a man, aged 52, was admitted to the University Hospital on March 27, 1931, under the care of Dr. Francis C. Wood. In March, 1930, he began to complain of fatigue. He had weighed about 200 pounds (90.7 Kg.) until this time, but began to lose weight rapidly with the onset of the fatigue until he became much emaciated at the time of admission to the hospital. In July, 1930, his right ankle swelled and became reddened, and in three weeks the left ankle was in the same condition; both were tender, with some increase of temperature, suggesting rheumatism. A heart murmur was detected about the end of November, 1930. The condition of the feet improved, but he had pain in the lower limbs, back of the neck and occipital region. Pain was felt in various parts of the body. He contracted a "cold" on March 25, 1931; on March 27 he appeared somewhat confused mentally; he had difficulty in swallowing and had slight convulsive movements of the fingers, then arching of the back and strong flexion of the fingers. The mouth became distorted, and he had ptosis of the right upper eyelid. He had complained of severe headache since early that morning. A diagnosis of a blood clot at the base of the brain was made by a physician outside the hospital.

Examination.—On admission, the patient's speech was difficult, and he was mentally clouded and irrational, but he understood questions and answered them. He was able to draw up each corner of the mouth. The pupils were small and stationary; i. e., they did not react to direct light. Examination of the eyegrounds gave negative results. At times, he had Cheyne-Stokes breathing. The heart was enlarged, and he had emphysema. He had ataxia in the left upper and lower limbs, shown by the heel-to-knee and finger-to-nose tests.

Course.—On March 28, he had a stiff neck, with Brudzinski's and Kernig's signs. A diagnosis of subacute bacterial endocarditis with an infected embolus in the brain near the base was made. These signs of meningeal irritation were

7. Schaeffer, Henri, and Blum, J.: Le syndrome de Parinaud, Arch. d'opht. **46**:351, 1929.

much lessened by lumbar puncture on March 29. A blood culture showed a gram-positive Streptococcus viridans (not Streptococcus mitis) organism in plates and broth. Fever had been present since admission. Lumbar puncture showed cloudy fluid, with 1,900 white cells, mostly neutrophils.

Lumbar puncture on April 2 gave a clear fluid, with 50 cells, of which 20 were polymorphonuclears and 30 lymphocytes; protein 4 units. The Wassermann and Kahn reactions were negative.

The right lower part of the face was paretic, and the tongue deviated slightly to the right when protruded.

On April 4, the mental condition was better. The patient died on April 15, 1931. The pathologic report showed subacute bacterial endocarditis.

Examination of the Eyes.—My ocular findings were obtained on two different days, April 4 and 9, and were the same each time.

The patient had paralysis of associated ocular movements to the left, paralysis of associated ocular movements upward, partial paralysis of associated ocular movements to the right, with much greater paralysis in the left internal rectus muscle, and marked paralysis of downward movement in the right eye. There was also paralysis of convergence.

Histologic Studies.—The marked paralysis of downward movement in the right eye may have been caused partly by the pronounced, though partial, degeneration of the left nucleus trochlearis, as the right trochlearis nerve has its origin on the left side. The superior oblique muscle assisted the inferior rectus muscle in downward movement of the eye, and the marked paralysis of the right superior oblique muscle, which must have been present, would have impaired downward movement.

It is singular that the trochlearis nerve, say the right, has its nucleus in close anatomic association with the nucleus of the left oculomotorius.

The brain stem was cut into blocks of a size to permit the embedding in celloidin, and serial sections were made from the level of the abducens nuclei to the entrance of the aqueduct into the third ventricle. I have not found any important lesion higher than the level represented in the section A244. The higher numbers in block A represent the higher levels. The lower numbers in block B represent the higher levels. About one of every ten sections was stained. Different methods were used with different sections. The cells of the nucleus oculomotorius showed no important alteration.

The lesions implicating the oculomotorius nerves seemed to begin about section A244 (fig. 1). At this level a small area of softening appeared just above the middle of the pes pedunculi of the left cerebral peduncle in the substantia nigra (corresponding about to figure 178 in Obersteiner's book[8]). (Section A230 was about the same level as A244.)

This area was considerably more distinct in section A229, and the softening here was nearer the inner border of the pes and implicated some of the fibers of the oculomotorius nerve. The pigmented cells of the substantia nigra were destroyed where the softening was intense. In sections A229 and 239 the oculomotorius fibers and their nuclei were well shown. The intense lesions were in the lower part of the oculomotorius nerve distribution. The area of softening became distinct in sections A139 and A120 (fig. 2), representing a level a little lower than Obersteiner's figure 178 (nearer fig. 177). Here it almost reached the inner border of the pes pedunculi. In section A149 another separate area of softening

8. Obersteiner, Heinrich: Anleitung beim Studium des Baues der nervösen Zentralorgane im gesunden und kranken Zustände, ed. 5, Vienna, Franz Deuticke, 1912.

began to appear near the left posterior longitudinal bundle, extended into it slightly, and was at the lower part of the oculomotorius nucleus (shown also in A120). This area was detected also at a higher level in moderate intensity in section A153. At section A239, the oculomotorius nucleus on each side appeared to be about normal. The area of softening near the left posterior longitudinal bundle observed in section A139 began in section A120 to divide the outer third of the posterior longitudinal bundle from the inner two thirds. The trochlearis nerve was well shown in section A78, passing around the aqueduct on each side. In section A75 (thionine stain) the trochlearis nucleus was shown well preserved on the right

Fig. 1 (section A236).—A small area of softening is seen just above the middle and inner part of the pes pedunculi in the substantia nigra.

side, but not on the left side, probably because of the softening that was close to the left trochlearis nucleus. Evidence of meningitis appeared in the interpeduncular space, but many of the cells had the appearance of phagocytic cells. The left posterior longitudinal bundle was greatly involved in the softening in section A49, and the area of softening was extensive.

The area of softening mentioned in sections A244 to A229 was close to the fibers of the left oculomotor nerve at their exit from the brain. In sections A229 to A213 the oculomotor fibers of each side were seen both inside and outside of the cerebral peduncles. The softening became increasingly extensive from section A172 to section A152, and still more so in section A120. No softening was

observed in the right cerebral peduncle or pons. Another area of softening began just below the left lateral lemniscus in section A140 and increased in size in sections of lower levels (seen also in A120).

Sections taken from the block above that designated as A did not show any softening.

In block B, which was the continuation downward of block A, in section B78 the left posterior longitudinal bundle was almost destroyed, and was destroyed at a lower level represented by section B127 (fig. 4), which corresponded to Ober-

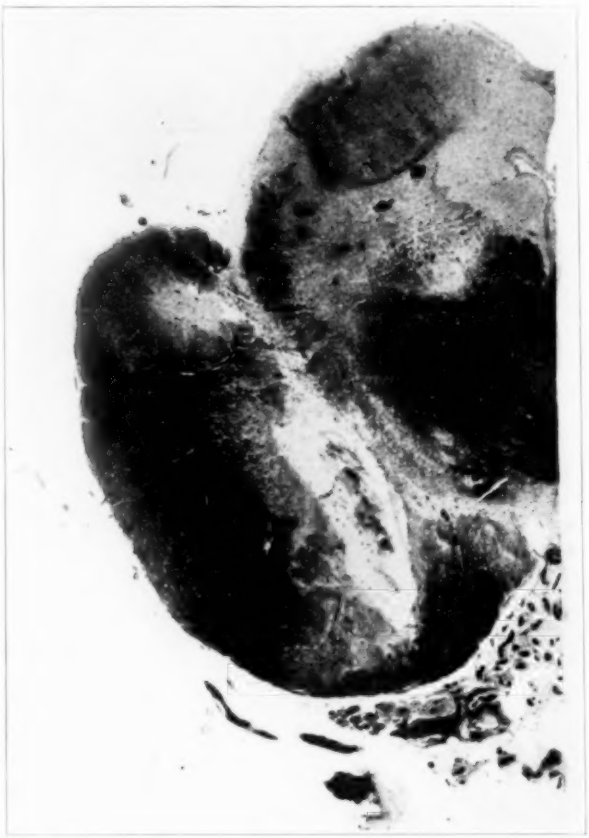

Fig. 2 (section A120).—Three distinct areas of softening are seen: one in the substantia nigra extending to the inner part of the pes pedunculi, one in the outer part of the pes pedunculi and one near the left posterior longitudinal bundle.

steiner's figure 174. In this section the exit of the trochlearis nerves was seen. The large area of degeneration mentioned was much less in extent in section B127. The left posterior longitudinal bundle was much less degenerated in section B273, which corresponded to Obersteiner's figure 172, and still less degenerated in section C200, although it was far from normal. The area of degeneration was small in section C192, and in section C179 was confined to the left posterior longitudinal bundle, and became slight in sections C160 to C155, which were a little below

Fig. 3 (section A69).—At the level of the trochlearis nerves.

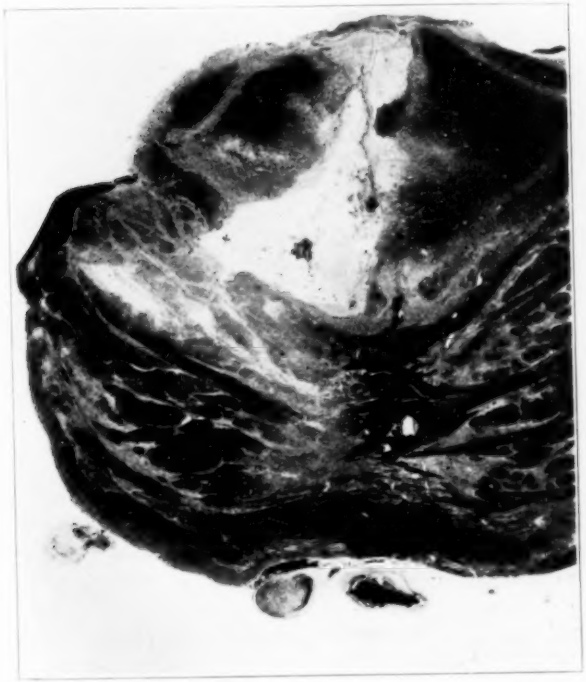

Fig. 4 (section B127).—Showing complete destruction of the left posterior longitudinal bundle.

Obersteiner's figure 172. The posterior longitudinal bundles in D80, which corresponded to Obersteiner's figure 170, appeared nearly equally well preserved on the two sides.

The abducens nucleus was shown in section F180 on each side, and by thionine stain each appeared to be normal; the nerve fibers were seen leaving each abducens nucleus in section F191.

COMMENT

Wilbrand and Saenger stated that the nucleus and root fibers of the oculomotorius receive their blood supply from the basilar artery, and at the bifurcation this artery at the anterior end of the pons gives off small branches which pass through the substantia perforata posterior and supply the greater part of the cerebral peduncle and the posterior part of the optic thalamus. The first of these vessels, the arteria peduncularis interna, supplies the inner portion of the pes pedunculi where the oculomotorius fibers have their exit. Van Gehuchten said that branches from the posterior cerebral artery enter the pes pedunculi and terminate in the substantia nigra. These are the vessels that were affected in my case, but in addition one or two of the vessels from the anterior end of the basilar artery which enter the pons at the raphe and supply the left side must have been involved, as the area of degeneration became more extensive in the upper part of the pons. The oculomotorius receives blood from the basilar and the posterior cerebral arteries, coming from different directions.

What is known regarding the corticonuclear tracts for associated ocular movements? It is accepted that there is a center for these movements in the frontal lobe and one in the posterior part of the superior temporal convolution. If these centers exist there must be separate tracts connecting them with the nuclei of the ocular nerves. It is well to examine the evidence that is offered for the existence of these tracts.

Dejerine[9] described aberrant fibers in the lower part of the cerebral peduncle at the level of the exit of the oculomotorius nerve which arise from the pes pedunculi: The pes profundus lemnisci (fig. 5 *PLp*), which is constant, and the pes superficialis lemnisci (fig. 5 *PLs*), which is relatively rare. He spoke also of postero-external aberrant fibers (fig. 5, *Fpe*), when they exist. All three bundles leave from the external second fifth of the pes pedunculi. The postero-external fibers pass around the outer border of the pes pedunculi, then in front of the internal geniculate body. Some of them join the median lemniscus; others pass through it and radiate into the anterior quadrigeminal tubercle.

Dejerine described degeneration of the aberrant fibers, shown by the method of Marchi, resulting from a lesion in the middle part of the

9. Dejerine, J.: Anatomie des centres nerveux, Paris, J. Rueff, 1901, vol. 2, p. 51, also figs. 376 and 377, p. 544.

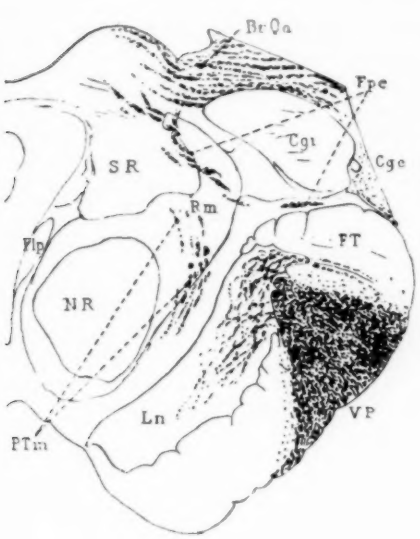

FIG. 374.

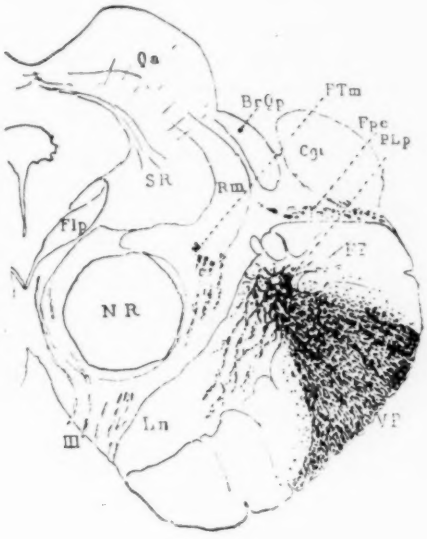

FIG. 375

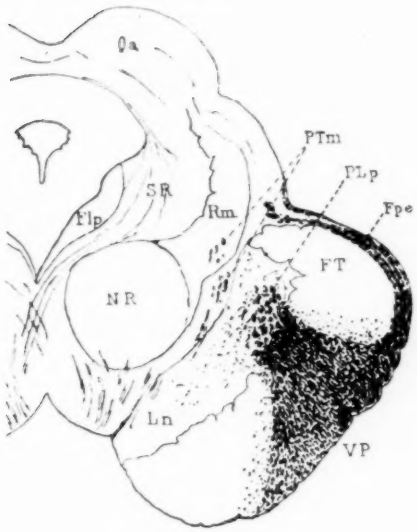

FIG. 376.

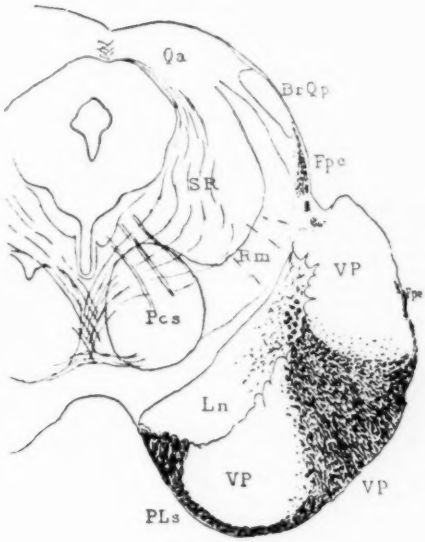

FIG. 377.

Fig. 5.—Plate from Dejerine's "Anatomie des centres nerveux." "Figs. 374, 375, 376, 377.—The aberrant fibers of the peduncular tract of the region of the cerebral peduncle: pes profundus lemnisci (*PLosp*) (figs. 375, 376, 377); pes superficialis lemnisci (*PLs*) (fig. 377); aberrant postero-external fibers (*Fpe*) (figs. 377, 376, 375, 374) in a case of degeneration of the central portion of the peduncular tract, secondary to a capsular focus, which destroyed the thalamic region, the posterior part of the posterior segment of the internal capsule and the adjacent part of the retrolenticular segment. (Marchi's method.)"

peduncular tract following a lesion of the posterior part of the posterior segment of the internal capsule and the adjacent part of the retrolenticular segment.

These aberrant fibers were discussed by Winkler.[10] He gave an excellent review of the knowledge regarding the pathways from the cerebral cortical centers to the motor nuclei of the brain stem, including those for the nerves of the ocular muscles, but he acknowledged that these pathways are not fully known. It is the opinion of many investigators that they cannot be identical with the pyramidal tract, because paralysis of the ocular muscles is not a common finding in cerebral hemiplegia. Winkler accepted Kappers' view that an intercalated system exists between the motor nucleus and the corticospinal tract, and that no fibers of this tract, with certain exceptions, pass directly to the motor nuclei of the brain stem. These exceptional fibers are those pertaining to the facialis and hypoglossus nuclei, and are involved at times in a complete lesion of the pyramidal tract. This intercalated system is much more important in the medulla oblongata than in the spinal cord.

Winkler was certain that the centrifugal paths that pass in the pes pedunculi and serve to innervate these intercalated systems have a separate course in the pons and medulla oblongata, distinct from that of the pyramidal tract in these parts. These fibers are known as aberrant pyramidal fibers, and credit is given to Dejerine and his pupils for having united them into a definite tract. These aberrant fibers of the pes pedunculi do not follow the pyramidal tract, but pass to the lemniscus and participate in the innervation of the intercalated systems. A certain number of them reenter the pyramidal tract.

These aberrant pyramidal fibers play an important rôle in the innervation of the nuclei of the facialis, trigeminus and abducens nerves, and are formed by several fasciculi described as: (1) the lateral pontile fasciculus of Schlesinger, (2) the accessory fasciculus of the lemniscus of von Bechterew, (3) the lateral foot lemniscus (Fuss-Schleife) of Flechsig, (4) the pes profundus lemnisci of Dejerine, (5) the aberrant proximal pedunculoprotuberantial fibers of Jumentiez and (6) the lateral part of the nebulous area (tache) in the central part of the lemniscus of Luchtmans. These are all synonyms for the same fasciculus, concerning which clarity has been brought by Dejerine, and to which he has given the name of pes profundus lemnisci. Schlesinger found that in several cases of syringomyelia the cavity had destroyed all the internal arcuate fibers, viz., the thalamopetal internal arcuate fibers, the secondary fibers of the nuclei of the acusticus nerve and all the

10. Winkler, C.: Opera omnia, Manuel de neurologie, Netherlands, de Erven F. Bohn, 1927, vol. 8, p. 10.

centripetal fibers of the lemniscus, so that in the cerebral peduncle at the level of the substantia nigra the lemniscus was deprived of fibers, but in the proximal part of the pons he found in the central part of the lemniscus a fasciculus of intact fibers, whereas the lateral and medial parts of the lemniscus were without fibers. This fasciculus of intact fibers was the stratum centrale lemnisci. This was composed of fibers of different caliber, some a very fine, nebulous area, and some coarse. When followed proximally this fasciculus approached gradually the foot of the peduncle, and where this emerged from the pons the fasciculus was found among the lateral fibers of the cerebral peduncle, hence the name lateropontile fasciculus. At still higher levels it joined the pyramidal tract in the foot of the peduncle.

This fasciculus may be recognized in normal preparations, leaving the pyramidal fibers to enter the lemniscus where the cerebral peduncle passes into the pons.

This fasciculus in the medulla oblongata, just above the motor decussation, is situated at the dorsal part of the lemniscus.

In the pes superficialis lemnisci of Dejerine are included the Bündel vom Fuss zur Haube of Meynert, the mediale Fuss-Schleife of Flechsig and the faisceau en écharpe of Féré.

In sections from the proximal part of the pons this bundle is situated in the medial part of the lemniscus, and in the cerebral peduncle forms the medial border of the pes pedunculi. This bundle, as Dejerine has shown by the method of Marchi, degenerates when the frontal operculum is destroyed. The pes profundus lemnisci has its origin in the temporal operculum. These two bundles innervate the motor nuclei of the trigeminus, abducens and facialis nerves chiefly by intercalated fibers.

The corticofugal fibers for convergence and vertical associated movements are uncertain. Winkler attributed them to the two pedunculi lemnisci of Dejerine, which reach the tegmentum by passing through the substantia nigra and come into association in the central gray matter with the intercalated apparatus necessary for innervation of these synergic functions. He assumed that the intercalated nuclei are as follows: the noyau en éventail for the movement of the eyes downward; the Westphal-Edinger nucleus for accommodation, convergence and contraction of the pupil; the nucleus of Darkschewitsch for the upward movement and closure of the eyes. He acknowledged that this scheme is far from proved.

I have not been able to find Dejerine's statement that the aberrant pyramidal fibers have their origin in the frontal operculum and the temporal operculum. This origin would seem to connect them with the frontal lobe center for associated ocular movements. He stated that he has seen these fibers degenerated by the Marchi method from a

lesion in the posterior part of the posterior segment of the internal capsule and the adjacent part of the retrolenticular segment. The latter area would suggest the origin in the temporal lobe center for associated ocular movements. However, the work of Mellus [10a] in excising small pieces of the motor cortex in the brain of the monkey showed that in the lower levels of the internal capsule all the degenerated pyramidal fibers coming from lesions of the facial as well as of the lower limb centers were well within the limits of the middle third of the posterior limb of the internal capsule.

Both the pes profundus lemnisci and the pes superficialis lemnisci of Dejerine have been described by numerous investigators under different names. Their existence must therefore be accepted.

Lhermitte and Kraus [11] found, in their two cases of paralysis of vertical associated ocular movement, the quadrigeminal tubercles, the posterior longitudinal bundle and the oculomotor nuclei intact. In their first case they observed a limited degeneration of the middle portion of each pes pedunculi, situated exactly symmetrically on the two sides. Some degenerated fibers could be followed into the tegmentum of the peduncle, where they were lost. They believed that this degeneration did not explain the paralysis of vertical gaze, as they had observed it in many cases of pseudobulbar palsy. The degenerated fibers they attributed to the faisceau génicule.

Their patient, toward the end of life, had bilateral hemiparesis. No illustrations are given in their paper, and it is impossible to determine whether or not the second external fifth of the pes pedunculi, which Dejerine believed is the part from which the aberrant fibers are derived, was degenerated.

Their second case was more satisfactory. They found degeneration only in the fibers of the internal fifth of the pes pedunculi high in its subthalamic portion. The lesion did not involve the transverse fibers arising in the lenticular nucleus and optic thalamus, which cross perpendicularly the cortical projection fibers that form the pes pedunculi. The degenerated fibers, they believed, belonged to the frontopontile tract, which arises in the frontal cortex and terminates in the ventral portion of the pons. They considered such a lesion of importance and one that should be sought in cases with the syndrome of Parinaud. This case is valuable in connection with the views of Dejerine and Winkler.

10a. Mellus, E. Lindon: Motor Paths in the Brain and Cord of the Monkey, J. Nerv. & Ment. Dis. **26**:197, 1899.

11. Lhermitte, J., and Kraus, W. M.: Note sur les lésions anatomiques du syndrome de Parinaud, Bull. Soc. d'opht. de Paris, 1924, p. 220.

Dejerine [12] disputed the existence of the frontopontile tract. He believed that the inner fibers of the pes pedunculi have their origin in the rolandic operculum, and he referred to three cases in which a lesion was found in the rolandic operculum and the adjacent part of the frontal operculum. The degenerated fibers were followed in serial sections through the knee of the internal capsule into the internal part of the pes pedunculi where it entered the pons.

One might ask whether the pes superficialis lemnisci could have been involved in Lhermitte and Kraus' second case. This fasciculus has not been described as separating from the pyramidal tract high in the subthalamic portion, but variations in the pyramidal tract are known to occur.

In a paper published in 1919, I expressed the view that supranuclear lesions could cause paralysis of the nerves supplying the associated muscles of the eyeballs. I referred especially to the ophthalmoplegia with involvement of the center for the internal rectus muscle by a supranuclear lesion in which convergence would be lost, and one with a lesion involving this center or the posterior longitudinal bundle below it, in which convergence would be preserved. In order that the paralysis of associated ocular movement may be persistent, the supranuclear lesion presumably must be near enough to the nucleus to catch the corticonuclear fibers from both sides of the cerebrum, as a lesion of one side might give a paralysis at first that might gradually be overcome by the vicarious action of the corticonuclear fibers from the other side of the brain. I emphasized that when a break occurs in the corticonuclear pathway above, but near the oculomotorius nucleus, no impulses can pass into this nucleus, and convergence is lost. Convergence may depend on the integrity of the nucleus of Perlia.[13]

I further emphasized that complete bilateral ophthalmoplegia might result from a lesion of the central pathways (corticonuclear fibers) near the nuclei, and regarding the case I reported in my paper, I diagnosed a lesion in or near the corpora quadrigemina causing paralysis of upward associated movement, marked but not complete paralysis of right lateral associated movement and slighter paralysis of left lateral associated movement.

Collier [14] expressed similar views in 1927. He also believed that ophthalmoplegia may be produced by interrupting only the supranuclear path by which incitations descend from the cerebrum to the oculomotor nuclei, as in lesions situated at the junction of the thalamus with the superior colliculus or when a lesion involves the posterior commissure,

12. Dejerine, J. J.: Anatomie des centres nerveux, Paris, J. Rueff, 1895, vol. 1, p. 602.

13. Perlia, quoted by Spiller (footnote 1 *c*).

14. Collier, J.: Nuclear Ophthalmoplegia, with Special Reference to Retraction of the Lids and Ptosis and to Lesions of the Posterior Commissure, Brain **50**:488, 1927.

which he believed is certainly an important decussation of the supranuclear path, since in a case that he recorded hemorrhage involving the left half of the posterior commissure caused complete loss of upward and downward movements of both eyes and loss of movement of both eyes to the right, with loss of convergence. Conjugate movement to the left was perfect. The hemorrhage just touched the anterior limit of the left superior colliculus and did not extend to the middle line of the commissure.

Collier said that with the exception of a comment of Gowers, to which he referred, the conception has not been hitherto formulated that a complete or a partial external ophthalmoplegia may occur from a lesion situated above the oculomotorius nuclei which entirely spares them. The specimen of the case with hemorrhage to which he referred does not appear to have been studied by microscopic sections. One might ask whether the postero-external aberrant fibers of the pes pedunculi described by Dejerine could have been involved in the tegmentum of the peduncle by this hemorrhage, as some of these fibers radiate into the anterior quadrigeminal tubercle.

Collier did not explain where the supranuclear fibers of the posterior commissure have their origin. He thought that the lesion must have completely divided all paths coming from above into the left superior colliculus, as well as those entering the posterior commissure from the left side and those crossing in the posterior commissure to the left side. From this case he concluded that it seems probable that the down-coming paths from the cerebrum for upward movement, downward movement and convergence cross in the posterior commissure, while those for lateral conjugate movement are situated more laterally and cross lower down, and yet he stated in the notes on the case that no movement of either eye was possible to the right. He made no reference to the aberrant fibers of the pes pedunculi. If one accepts the double corticonuclear pathways, one through the posterior commissure and one by the subthalamic aberrant fibers of the pes pedunculi, it is possible to postulate a lesion implicating both systems by the hemorrhage in Collier's case. Collier did not present a microscopic study and did not state the full extent of the destruction of the brain in his case, but in his comments in closing the discussion on his paper he said that the lesion in the case was subthalamic.

This supposition of double pathways in each cerebral hemisphere is supported by the case reported by Dereux.[15] Dereux, in his thesis (1926), reported a case in which there was paralysis of upward and downward movement with bilateral ptosis, but lateral movements seem to have been preserved. He explained this by a supranuclear lesion. His study of all the cases that he could find in the literature of such

15. Dereux, J.: Paralysie verticale du regard, Thèse de Paris, 1926.

paralysis with necropsy led him to conclude that the results were rather disappointing. In by far the greater number the lesion was a tumor, and conclusions drawn from these are unreliable.

Dereux's case had previously been reported by Vincent from its clinical aspect, but microscopic sections were studied by Dereux. The lesion was a small hemorrhage in the subthalamic region. It was adjacent to the central motor tract from the external nucleus of the optic thalamus into the subthalamic region, where it reached the third ventricle and involved fibers of the posterior commissure and terminated in the middle portion of the cerebral peduncle, where it did not reach the aqueduct. He did not think that the lesion in the optic thalamus or in the subthalamic region could have caused the vertical paralysis of gaze, but he did not consider Dejerine's aberrant fibers of the pes pedunculi. At the entrance of the aqueduct into the third ventricle the lesion destroyed a part of the posterior longitudinal bundle and the fibers of the posterior commissure, and to this he attributed the vertical paralysis of gaze. He dismissed the possibility of the subthalamic lesion in his case producing the vertical paralysis of gaze by referring to certain cases in the literature in which subthalamic lesions did not produce similar associated ocular palsy.

Froment, Dechaume and Colrat[16] asserted that there are two corticonuclear oculomotor paths in each cerebral hemisphere:

1. The anterior tract, having its origin in the rolandic zone, passes in the internal part of the foot of the peduncle, and from there to the median lemniscus, where it mingles with aberrant peduncular, pontile and bulbopontile fibers of the pyramidal tract. It is the oculogyric and cephalogyric tract, and after decussation in the median line gives fibers to the oculomotor nuclei, i. e., to the oculomotorius nuclei bilaterally, the trochlearis nucleus of the same side and the abducens nucleus of the opposite side, also to the facialis and the spinalis accessorius nuclei of the opposite side and to divers motor centers of the cervical gray matter. It is the corticonuclear path of voluntary motion.

2. The posterior tract is long, coming from the occipital cortex; through the optic radiations it reaches the anterior quadrigeminal tubercle, where it seems to form a relay, then descends in the cerebral peduncle and gives fibers to the oculomotorius nucleus of the same side. After decussating at the median line with the corresponding tract of the opposite side at the level of Meynert's decussation, it descends in the prelongitudinal bundle and gives fibers to the trochlearis and abducens nuclei of the opposite side, to the facialis and spinalis accessorius nuclei and the cervical nuclei of the opposite side (cephalogyric

16. Froment, J.; Dechaume, J., and Colrat, A.: Deux observations anatomocliniques de paralysie des mouvements associés de latéralité des yeux, Rev. d'otoneuro-opht. **8**:713, 1930.

nuclei). There is little anatomic evidence to justify this description, but it offers an explanation that sounds reasonable. One must accept the view that in some such manner the posterior cortical center for associated ocular movement is connected with the nuclei of ocular nerves, and it may be that this connection is via the posterior cerebral commissure. Further studies may afford the proof.

Paul van Gehuchten [17] cited Muskens as believing that the descending fibers arising in the corpus striatum have a relay (synapse) in the nucleus of the posterior commissure. The fibers arising in this nucleus, commissuromedullary fibers, cross the median line to enter the opposite posterior longitudinal bundle, and these fibers control the lateral movement of the eyes. This hypothesis is based on a certain number of experiments.

It is argued that the corticonuclear pathway for ocular movements cannot be in the pyramidal tract because paralysis of associated ocular movements does not occur in hemiplegia of cerebral origin. It is not uncommon to have deviation of the head and eyes toward the side of the lesion in the onset of hemiplegia, and this is from paralysis of associated lateral movement of the eyeballs toward the side opposite the lesion, with overaction of the corresponding tract from the sound cerebral hemisphere. This paralysis is of brief duration, and the recovery is attributed to the compensatory action of the unaffected similar corticonuclear ocular pathway of the sound side. Possibly the assumption of two pathways, one from the frontal center and one from the temporal center, may explain better the early restoration of lateral associated ocular movement in hemiplegia, in that the temporonuclear tract assumes the function of the damaged frontonuclear tract. A single lesion could paralyze both these tracts if it were near the oculomotorius nucleus and involved these tracts near this nucleus.

It is a question whether a unilateral lesion of the corticonuclear pathway near the oculomotor nucleus can cause persistent paralysis of associated upward or downward ocular movement, or whether the lesion must be in the posterior cerebral commissure, as Collier seems to have thought, and catch the fibers from each cerebral hemisphere in order to produce a persistent paralysis. The upward and downward movements are more definitely bilateral, as I [18] pointed out in my paper on isolated movements of the eyeballs, than are lateral ocular movements, and I explained this on a phylogenetic basis; therefore, complete disruption between the cortical centers and ocular nuclei of one side might produce a persistent impairment, if not a complete paralysis, more likely in lateral movements than in vertical movements.

17. van Gehuchten, Paul: Un cas de paralysie latérale du regard par lésion protubérantielle: Contribution à l'étude des voies oculogyres, Rev. d'oto-neuro-opht. **8**:701, 1930.

Muskens [18] referred to the work of van Gehuchten, Cajal, de Lange and Castaldi, who agreed in the view that nuclei exist about the posterior commissure, which have been proved to be of peculiar significance in relation to forced movements, and which are now recognized to be relay centers for the ascending secondary vestibular connections. It appears that these nuclei are connected with a large number of ascending vestibular fibers but give rise to a much smaller number of descending fibers that are possessed of a functional significance far superior to their anatomic size. Muskens asserted that forced movement in the horizontal plane in animals is in man represented by conjugate deviation, and, in man, paralysis of associated movement is nothing but a lesser degree of conjugate deviation (personal communication from the author).

The case that I have presented is the only one of paralysis of associated ocular movements, so far as I know, in which microscopic serial sections from the level of the abducens nuclei to the beginning of the third ventricle have been studied, and in which the views of Dejerine and Winkler have been considered in the interpretation of the lesions found. There are weak points in this interpretation that have not been ignored, and yet it affords the best explanation of the manner in which the lesions found could explain the symptoms. The area of softening in the left substantia nigra begins precisely at the level where the pes profundus lemnisci has its origin in the external second fifth of the pes pedunculi (fig. 1), at the level of the exit of the oculomotorius nerve. This area of softening rapidly extends inward and may have involved the pes superficialis lemnisci where it passes to the median lemniscus (fig. 2). The postero-external aberrant fibers are not asserted to pass to the oculomotorius nuclei, but as they are represented in Dejerine's plate (fig. 5), it is possible that they have a connection with these nuclei. The area of softening mentioned in section A149, near the left posterior longitudinal bundle (fig. 2), may have affected these fibers in their control of the oculomotorius nuclei; it may have impaired their control of the trochlearis nuclei as it is above these nuclei, and it may have implicated fibers of the temporonuclear tract near the ocular nuclei. The postero-external aberrant fibers may have been involved by the area of softening described in sections A140 to A120 just below the left lateral lemniscus. These fibers could have been involved in this area as they passed from the outer border of the external fifth of the pes pedunculi into the tegmentum of the cerebral peduncle. The effect of destruction of the vestibular fibers on the left side is uncertain.

18. Muskens, L. J. J.: A Discussion on the Part Played by the Supravestibular Connections in Decerebrate Rigidity, J. Physiol. **64**:308 (Feb. 10) 1928.

PARALYSIS OF LATERAL ASSOCIATED OCULAR MOVEMENT

Paul van Gehuchten,[17] in discussing the formation of the posterior longitudinal bundle, referred to van der Schueren's statement that these fibers may be divided into the vestibular and the nonvestibular fibers. The vestibular fibers arise chiefly in the triangular nucleus, the descending nucleus and Bechterew's nucleus. The fibers from Bechterew's nucleus are ipsolateral. They occupy the loose lateral part of the posterior longitudinal bundle and form the vestibulomesencephalic fasciculus, described by van Gehuchten. The existence of this tract has been confirmed by Muskens. Van Gehuchten has seen it degenerated from a lesion confined to Bechterew's nucleus.

The fibers arising in the triangular and descending nuclei essentially decussate across the raphe and then divide into ascending and descending fibers. The ascending fibers form a connection with the nuclei of the trochlearis and oculomotorius nerves. They are in the compact zone of the posterior longitudinal bundle. They have been confirmed by Muskens. He believed that the fibers from the triangular nucleus decussate to the other side from the lower part of this nucleus to the level of the decussation of the fibers of the trochlearis nerve. They assist in the formation of the internal zone of the posterior longitudinal bundle.

The nonvestibular fibers of van der Schueren are all descending fibers. They arise in the reticulated cells of the mesencephalon (supralateral nucleus of Flechsig-Held, interstitial nucleus of Cajal and Darkschewitsch, the periaqueductal cells and reticulated cells of the bulb and pons).

Muskens described three descending fasciculi: the commissural medullary fasciculus, the interstitial spinal fasciculus and the lateral fasciculus described by Probst. The first two fasciculi are situated in the compact part of the posterior longitudinal bundle. They arise in the commissural nucleus and in the interstitial nucleus. In front of the posterior longitudinal is the longitudinal predorsal fasciculus. This fasciculus, according to the researches of Held, Cajal, Mungs, Pavlov and van Gehuchten, appears to consist entirely of descending fibers arising in the corpora quadrigemina. Van Gehuchten called this the tectobulbar fasciculus.

It is known that in the monkey, and probably in man, the internal rectus muscle is innervated by uncrossed fibers, i. e., fibers from Bechterew's nucleus.

Experimental studies have shown that the abducens nerve does not send fibers to the posterior longitudinal bundle. The triangular nucleus is the most intimately associated with the nucleus of the abducens nerve, and involvement of this nucleus in its internal portion causes paralysis of associated lateral movement. This view is supported by

Winkler. He regarded the nucleus of Fuse as a part of the triangular nucleus, and it is the center regulating the tonic innervation of the ipsolateral external rectus muscle and of the opposite internal rectus muscle through the posterior longitudinal bundle. Implication of Fuse's nucleus produces paralysis of lateral associated ocular movement toward the side of the lesion and conjugate deviation of the eyes away from the side of the lesion in man, but not in the cat, dog or rabbit.

Froment, Dechaume and Colrat [16] cited a number of cases that seem to support the existence of a center in or near the abducens nucleus for the coordination of lateral movements of the eyeballs, but they also cited cases in which the abducens nucleus was intact. They referred to a case reported by them in 1928, in which right oculogyric paralysis was caused by a pontile tubercle that implicated the posterior longitudinal bundle in the middle of the pons but did not involve the abducens nucleus. In case 1 of their paper, published in 1930, a glioma chiefly in the upper left side of the tegmentum of the pons destroyed the left posterior longitudinal bundle without involving the abducens nucleus. Clinically, there was left oculogyric paralysis. They asserted that for paralysis of lateral associated ocular movements there must be a lesion of the abducens nucleus or of its vicinity, or one of the posterior longitudinal bundle. They did not think that a lesion of the posterior longitudinal bundle alone is able to explain the paralysis of lateral associated ocular movements, and that the abducens nucleus or some structure in its vicinity must exert an influence through the posterior longitudinal bundle, and yet they reported two cases in which the abducens nucleus was intact.

It would seem to me that for paralysis of lateral associated ocular movements the lesion is usually near the abducens nucleus and probably involves the posterior longitudinal bundle. The case [16] of ophthalmoplegia internuclearis anterior that I published in 1924, the only one with a necropsy in the literature, showed that extensive destruction of both posterior longitudinal bundles, if near the oculomotorius nucleus, may cause a complete loss of action of the internal rectus muscle in both eyes for right and left lateral movements, but in the associated movement of convergence both internal recti muscles may act, and also the external rectus muscle, acting alone, may retain its function on each side. The explanation for these phenomena may be that only a lesion near the abducens nucleus, unless the median lemniscus is degenerated in higher levels of the pons, will implicate that portion of the aberrant fibers of the pes pedunculi that has to do with the innervation of the abducens nucleus. Implication of the posterior longitudinal bundle is needed also for paralysis of associated lateral movement. It is not

necessary to assume that a lesion must be in the location mentioned because it involves a supranuclear center for associated lateral movement. I find no evidence for such a center.

In the case reported in this paper the degeneration was extensive in the upper part of the left side of the pons and extended downward nearly to the upper portion of the fibers of the trigeminus nerve at their exit from the pons. The aberrant fibers from the left pes pedunculi, which at this level are in the median lemniscus, were surely involved in this area of degeneration, and with them were the fibers destined for the nucleus abducens. In the right side of the pons none of the aberrant fibers from the right pes pedunculi were involved, and the right posterior longitudinal bundle was not degenerated. The patient had partial paralysis of associated ocular movement to the right, with much greater paralysis in the left internal rectus muscle.

ABSTRACT OF DISCUSSION

Dr. Frederick Tilney, New York: Dr. Spiller's important and well reasoned case brings up again the subject of combined head and eye movements. Obviously, the detailed understanding of the neural mechanisms controlling these movements is far from final. The exact identification and localization of the controlling centers and even of the connecting tracts still leave much to be desired. Obviously, also, the progressive up-building of these combined movements is represented by a definite series of evolutionary horizons. Many critical phases in this up-building may be easily discerned. The introduction of the vertebrate neck with the development of a mobile head represents one important phase. The assumption of motor control by the neocortex in the class of mammals is another. In stages of animal life prior to the appearance of the neocortex, eye and head movements were fundamental responses arising from the necessities of visual pursuit and spatial orientation. After the acquisition of the neocortex in mammals, these responses not only remained equally fundamental, but became more highly organized because of the expansions in visual capacity.

As Dr. Spiller points out, neocortical centers in the frontal lobe for ocular movements have long been recognized, especially as the result of experimental investigations on apes (Horsley and Beevor, 1890, orang; Grunbaum and Sherrington, 1901, chimpanzee). Similar centers have also been identified in the temporal and occipital lobes. Some years ago, in collaboration with Adrian Lambert, I was able to locate an area in the superior temporal convolution in baboons, stimulation of which produced conjugate movements to the opposite side.

The predominant result of experiments on the cortical centers has been the production of movements for lateral gaze. Movements for vertical gaze have been for the most part absent. Risien Russell's experiment lends support to Hughlings Jackson's explanation of this failure to produce experimental upward or downward movements of the eyes. But this explanation may be carried a step further. Vertical ocular movements might conceivably be regarded as one of the later horizons in oculocephalogyric control. An added incentive to it may well have been coincident with the assumption of arboreal life by the early primates, when the ability to look aloft and downward became most necessary. This new primate adaptation was associated with a shortening of the neck and the first preliminary steps toward assuming the erect posture. Thus, the relative newness

of these vertical ocular movements would, by contrast with the great antiquity and general prevalence of lateral movements in mammals, explain the predominance of the neocortical areas for control of lateral gaze. A definite center in the temporal lobe has not yet been thoroughly established, although there is considerable evidence in favor of its existence. If present, it is probably related to spatial orientation and the sense of hearing. An occipital center is still more hypothetic, but I believe that there is some evidence suggestive of such a center and that it is functionally associated with the oculomotor requirements of the binocular, stereoscopic vision of man, especially as these requirements have to do with the downward and inward rotation of the eyeballs.

Concerning the corticonuclear tracts, which have been called by many names and by the Dejerines "aberrant fibres of the peduncular pathway," it is perhaps unfortunate to designate them as "aberrant pyramidal fibers." By functional implication they have a pyramidal significance, but the structure of the pes profundus contingent, at least, has a much closer topographic association with the mesial fillet than with the pyramid. That they represent a distinctive system apart from the pyramidal system Dr. Spiller has clearly shown by the absence of their involvement in many cases of hemoplegia. This fact also may be illustrated by certain oculogyric spasms due to encephalitis in which no other somatic muscles are involved and by some of the oculometer spasms incident to petit mal. I am in accord with Dr. Spiller in believing that a lesion of the subthalamic contingent of these aberrant fibers from the pes profundus may produce paralysis of the vertical eye movements.

Dr. Spiller's case, because the serial study is limited to the brain stem, cannot throw further light on the cortical centers controlling ocular movements. It gives considerable information concerning the corticonuclear connections implicated in this activity. It is unfortunate that, as is the case in most clinicopathologic studies, the lesion is too extensive or too diffuse to permit the application of the most effective methods for tracing fiber connections.

The early history of the patient's illness indicates a systemic infection affecting the joints and endocardium. Subsequently, streptococcemia complicated apparently by diffuse meningo-encephalitis developed. The neurologic symptoms, aside from the mental disturbances, slight convulsive movements, ataxia, meningeal irritation and ptosis, are all well explained by lesions involving the corticonuclear contingents of aberrant fibers, although the case does little in actual identification of these fiber systems themselves.

As Dr. Spiller indicates, there are weak points in this interpretation. But clinicopathologic methods alone cannot hope to straighten them out. For that matter, it seems improbable that any single method by itself can be expected to solve such problems as these. Applied separately and without critical correlations, the experimental, embryologic and comparative methods will not yield wholly satisfactory results. What is needed is a well conceived cooperative effort that will utilize the advantages of all methods in dealing with problems of this magnitude.

However, accepting the premises already advanced as to the oculomotor centers in the cortex and their corticonuclear connections, Dr. Spiller's interpretation is the best explanation of the manner in which the demonstrated lesions produced the symptoms.

NERVE DEGENERATION IN POLIOMYELITIS

IV. PHYSIOLOGIC AND HISTOLOGIC STUDIES ON THE ROOTS AND NERVES SUPPLYING PARALYZED EXTREMITIES OF MONKEYS DURING ACUTE POLIOMYELITIS

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In poliomyelitis there is a close and evident relation between permanent functional loss and its underlying lesions. The residual paralysis which occurs in the typical case is readily attributable to the death of groups of anterior horn neurons. But with stages intermediate between the first association of the virus with the cell and the final damage wrought we are not familiar. Shortcomings in our knowledge concerning the living condition of the nerve cell make difficult the interpretation of appearances seen in fixed and stained preparations. When affected segments of the spinal cords of monkeys killed during the preparalytic stage and during the first days of paralysis are contrasted, there is often shown the rapid destruction of many nerve cells. Others of the affected segments, damaged in varying degree yet retaining a semblance of life, are common, their number varying in the individual case. It is in such cells that Covell,[1] working in this laboratory, discovered the presence of intranuclear inclusions apparently specific for the disease, an observation later confirmed by Hurst.[2] In this situation, also, attempts have been made to classify the stages in destruction of chromidial substance, neurofibrils and mitochondria, with the hope of securing a better understanding of the mode of action of the virus. It is our belief that this line of investigation will be strengthened by a

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1. Covell, W. P.: Nuclear Changes of Nerve Cells in Acute Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **27**:927, 1930.

2. Hurst, E. W.: The Occurrence of Intranuclear Inclusions in the Nerve Cells in Poliomyelitis, J. Path. & Bact. **34**:331, 1931.

thorough study of the parts of nerve cells which can be most conveniently examined by physiologic methods, namely, their fibers in spinal roots and peripheral nerves.

This investigation naturally fell into three parts (supplemented by the papers of Covell and O'Leary, and of Covell): The first provided the essential normal basis by a study of the physiologic properties of normal nerves of a monkey. In the second, and for purposes of comparison, we investigated the relation between the time of disappearance of the action potential in normal nerves severed from their cells of origin and the histologic appearance of the fibers. The latter experiments were conducted on the cat, a typical mammal more available in quantities than the monkey. We are now concerned with acute poliomyelitis: the mortality of the cells injured by the virus, the nature of the changes in function of the fibers involved and the rate of disappearance of conductivity in the degenerating fibers of roots and nerves as compared with that of normal nerves cut off from their cells of origin.

MATERIAL AND METHODS

Thirty Macacus rhesus monkeys were employed in the experiments. With the assistance of Dr. William B. Brebner they were given intracerebral or intrasplenic (two cases) inoculations of a mixed virus strain secured through the kindness of Dr. Simon Flexner, of the Rockefeller Institute.[3] Temperature and behavior were recorded during the period of incubation and the acute stage of the disease. The progress of paralysis in the extremities was also observed and recorded. At the desired stage, the monkeys were killed under ether anesthesia by bleeding from the heart. In certain monkeys galvanic stimulation was applied to typical nerves, to spinal roots and to the cord above the affected levels to determine the site of functional loss. Control segments of nerves were fixed immediately after excision, and the remainders were placed in iced Ringer's solution for study with the cathode-ray oscillograph, after which they also were fixed. The parts for cytologic study were cut into segments, affixed to glass rods and immersed in a variety of fixatives: osmic acid for study of the myelin sheaths; ammoniated alcohol for the Cajal-Ranson procedure for axons, and Cajal's formaldehyde-pyridine-manganese mixture for infundibular membranes. Typical nerves in successively advanced stages of paralysis were prepared by the Marchi method. To detect proliferative changes in the Schwann cells and provide for the possible necessity of studying cell infiltration along the course of nerves and roots, various chrome sublimate combinations were used.

The method of histologic investigation employed does not differ from the accepted procedure in the investigation of problems concerned with degeneration and regeneration in peripheral nerves. Cajal's[4] masterly exposition of this

3. This strain of virus was used throughout the series. Tremors usually appear five days following intracerebral inoculation, paralysis on the sixth or seventh day.

4. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928.

subject and the noteworthy contributions of Ranson [5] and others are so well known that further comment is unnecessary. In one respect we have extended this information, by the correlation of histologic change in degenerating fibers with the depression and disappearance of the action potential.

Though the degenerative changes in the fibers of peripheral nerves and spinal roots are continuous and progressive, they may for convenience be divided into three stages: early, moderately advanced and advanced. The criteria employed were based on the descriptions by Cajal of degeneration in severed nerves: early degeneration is distinguished by thinned myelinic segments in the region of the nuclei of Schwann's cells (Cajal [6]), increased width of the incisures and varicose appearing axons; the moderately advanced stage by fragmentation of myelin, hyperplasia of Schwann's cells and segmented granular axons, and the advanced stage by metamorphosis of the fiber into a syncytial mass of Schwann's cells containing within it globules of myelin of various sizes, occasional vesicles in which granular axonic fragments may be seen, and frequent small groups of neurilemma nuclei. The advanced stage has only been noted by us in fibers of medium and large size.

The physiologic aspects of the study involved the use of the cathode-ray oscillograph in association with an amplifier as a recording device. This instrument has been extensively employed in physiologic studies of nerve and muscle (Gasser, Erlanger, Bishop and Heinbecker). This is its first utilization in an investigation of disease. The technical details of its use are now well established, but for those whose interests are not primarily in physiology a brief explanation will be given. The cathode-ray oscillograph is a thermionic vacuum tube of a type in which a beam of electrons is projected onto a fluorescent screen painted on the end of the tube. The electron beam on its course to the screen passes between two pairs of plates set at right angles to each other. A potential applied to the vertical pair of plates deflects the beam in the horizontal plane and the focused electrons move across the screen as a line. The speed of this movement across the screen can be controlled and measured. The line serves the same purpose as a base line in a kymographic record. By means of a circuit breaker or double key, a stimulus can be synchronized with any point in this deflection. This stimulus together with the resultant action potential from the nerve is applied to the other pair of plates, which causes a deflection of the electron beams at right angles to the base line. A visible standing-wave picture results, which can be exactly repeated as frequently as the tissue will respond and can be recorded photographically.

It is known that when a nerve fiber becomes active there is a potential change at the site of activity. This activity is propagated along the nerve fiber. Recording electrodes placed on the nerve will serve to convey the potential change of activity to the amplifier-oscillograph combination and cause a deflection of the electron beam. As different fibers within a complex nerve trunk have different conduction rates, it is readily understood that when a group of fibers is activated by an electrical stimulus and the activity propagated along the axons, those in which the propagation is most rapid will produce a change in the recording electrodes before the more slowly conducting axons. As a consequence, from a complex nerve trunk the complete conducted action potential record will consist of a series of waves, the thresholds, time relations and amplitudes of which, under specified experimental conditions, give significant physiologic data as to the fiber content of the nerve and the state of activity of its fibers. By correlation between

5. Ranson, S. W.: Degeneration and Regeneration of Nerve Fibers, J. Comp. Neurol. **22**:487, 1912.

6. Ramón y Cajal (footnote 4, fig. 17).

the recorded potential and the cross-section of the nerve trunk as revealed in osmic acid-stained sections, it has been possible to show that four groups of waves are assignable to the four types of fibers recognizable anatomically. The different thresholds of each of the fiber types permits one group of waves after another to be elicited by gradually increasing the strength of the stimulating current. Consequently, it is possible to study the fiber types essentially responsible for each wave, separately, and to determine in them deviations from the normal.

For convenience of reference, the four components have been named the A, B_1, B_2 and C waves (Heinbecker, 1930). The fibers responsible for the A component are the large, thickly myelinated ones. The B_1 component includes primarily the somewhat smaller and frequently somewhat more thinly myelinated fibers. The fibers responsible for the B_2 potential are the finest, myelinated ones found in the nerve. Unmyelinated fibers give rise to the C potential.

HISTOLOGIC STUDIES

Myelin and Neurilemmal Sheath Alterations in Peripheral Nerve Fibers of Paralyzed Extremities.—For the study of the early stages of acute poliomyelitis in monkeys, nerves from the affected extremities of animals killed during the preparalytic stage, and on the first, fourth and fifth days following the onset of paralysis were available.

Monkey 41 was killed on the appearance of tremors, seven days after the intracerebral inoculation of the virus, and the left femoral, left deep radial, sciatic and phrenic nerves were removed for oscillographic record and histologic study. No deviations from the normal were detected (compare figs. 2, *2* and 2, *1*). Similarly, an assortment of nerves from the upper and lower extremities of a monkey killed on the first day of paralysis were found to be functionally and histologically normal. It would, therefore, appear that the first significant failure to function involves the cell body, or synapse, rather than the axon.

In a monkey paralyzed in the upper extremities for four and one-half days, isolated, thickly myelinated fibers of the left femoral nerve showed unmistakable early degenerative changes (fig. 1, *3*). Occasional fibers had assumed a sacculated appearance, and in others there was evidence of slipping of the myelin at the nodes. Throughout the nerve, the infundibular membrane remained unchanged. The right and left radial nerves, which were removed from the extremities that had been paralyzed for a shorter length of time, showed no alterations.

After five days of paralysis (monkey 84) the right peroneal nerve, as well as the right second sacral motor and sensory roots, were fixed in osmic acid following study by the cathode-ray oscillograph. Although the stage of paralysis was but slightly advanced as compared with monkey 62, evidence of impaired function was much more manifest. Degenerative changes were apparent in many large and medium-sized myelinated fibers. Alterations in the large fibers were most frequently

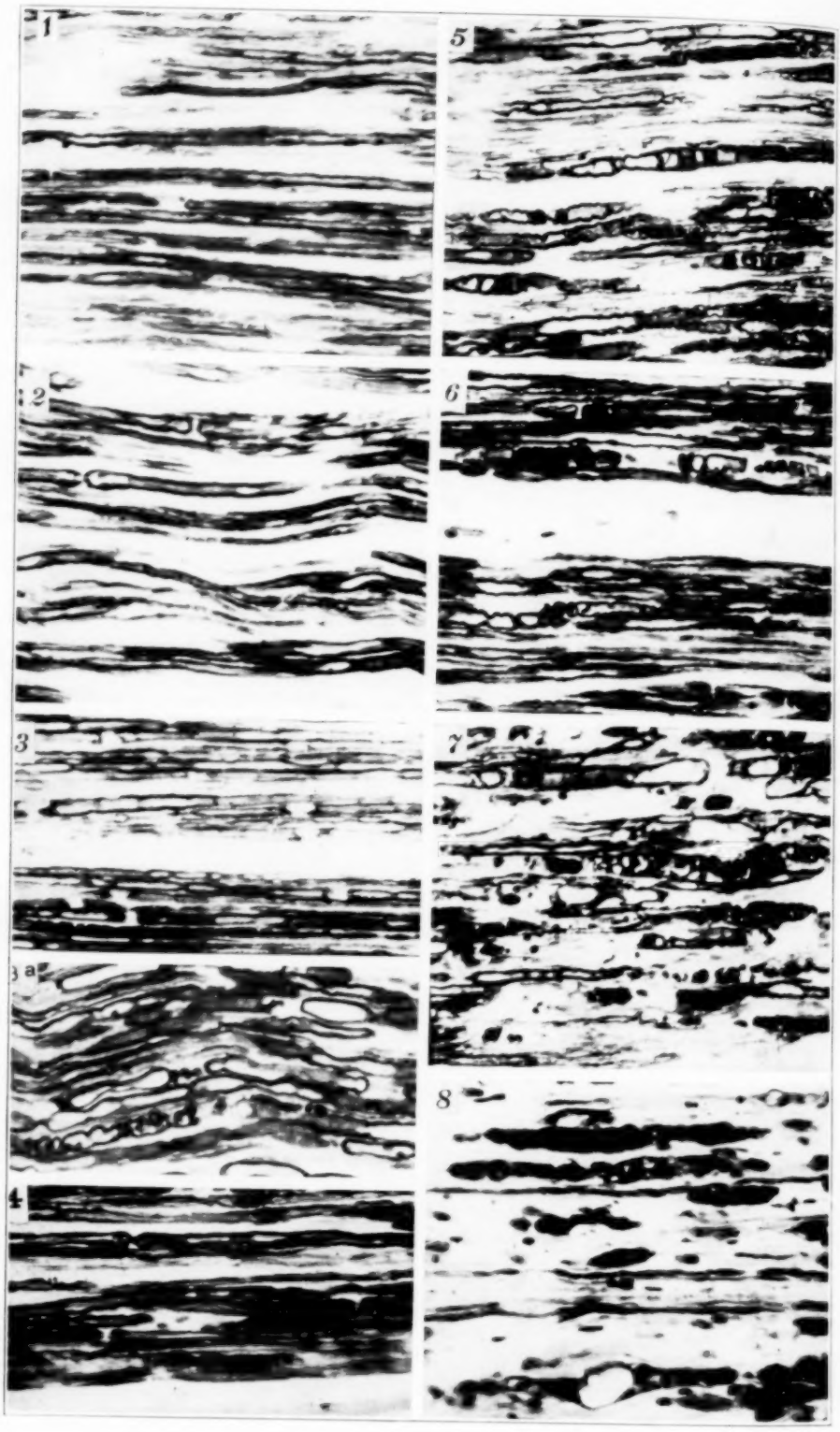

Figure 1

EXPLANATION OF FIGURE 1

Fig. 1.—Longitudinal sections of peripheral nerves from affected cord segments at successive stages following the appearance of paralysis; osmic acid fixation. *1* shows the femoral nerve from a normal monkey; *2*, the left sciatic nerve, preparalytic stage, all fibers of which are normal; *3*, left femoral nerve at four and one-half days' paralysis, illustrating increased width of the nodes and beginning segmentation of the myelin sheaths of large fibers; *3a*, right peroneal nerve of a monkey killed four and one-half days following the onset of paralysis. Moderately advanced degenerative changes were observed in a considerable number of large, myelinated fibers. *4* shows the right ulnar nerve after seven days of paralysis. Complete segmentation of myelin in large fibers is a not uncommon occurrence. Fine and medium-sized myelinated fibers are unaltered. *5* shows the right deep radial nerve at ten days of paralysis. The greater proportion of large, myelinated fibers showed sheath segmentation. Fine, myelinated fibers appeared to be unaltered. *6* shows the left posterior tibial nerve at fourteen days of paralysis. Large fibers in an advanced state of degeneration are not uncommon, but it is evident that a good proportion remained unaltered, particularly the fine, myelinated ones. *7* and *8* represent the right sciatic (eighteen days) and the right deep radial (thirty-three days) nerves, the latter having but few normal fibers, principally of the smaller, myelinated variety. Zeiss 8 mm. Oc × 10, 275 diameters.

encountered; they varied from increased width of the nodes and amplification of the incisures (thus lending to the fiber a vesiculated appearance) to complete fragmentation of the myelin sheath into digestive chambers joined together by hypertrophied sheath cells containing smaller spherules of myelin. In the medium-sized, thin-sheathed fibers complete fragmentation was seen occasionally, but changes were usually confined to vesiculation. Fine, myelinated fibers appeared to be unaffected.

Monkey *22* illustrates the conditions that were present in peripheral nerves on the seventh day of paralysis. In the right ulnar nerve some large, thickly myelinated fibers were observed in every stage of degeneration. About two thirds of them, however, were found to be perfectly normal, and presumably the large sensory fibers were a part of this group. A few of the medium-sized, relatively thinly myelinated and fine, myelinated fibers showed early degenerative changes. A photomicrograph (fig. 1, *4*) indicates the proportion of degenerating to normal fibers in this nerve.

At approximately the same stage of paralysis (monkey *66*, six and one-half days), formaldehyde-pyridine-manganese preparations were made for the study of infundibular membranes in typical nerves supplying paralyzed extremities. A few large fibers in each nerve showed pronounced granular degenerative changes in the infundibular membranes ("heaped irregular clots" of Cajal) comparable to the alterations figured by Cajal three days after section of the cat's sciatic nerve.[7]

In a monkey with total paralysis of the extremities for nine days (monkey 59), the right and left sciatic and radial nerves were taken for study. In the left sciatic and radial nerves, relatively few large and medium-sized myelinated fibers were in the advanced stage of degeneration, but in a considerable number, approximately one fourth of the total, the degenerative changes were moderately advanced. Occasional fragmented, fine, myelinated fibers were also observed. In the right sciatic, alterations were confined to the heavily myelinated fibers of a single peripheral bundle, each of which was in an advanced stage of degeneration; all other fibers appeared histologically normal. Segments of the same nerves were fixed in formaldehyde-pyridine-manganese. Only in the left radial nerve were changes apparent in the infundibular membranes; in casual vesiculated fibers of the large myelinated type, these were reduced to mere rings of a granular deposit about the sheath. If comparison is made between the histologic changes observed in these nerves (nine days' paralysis) and the posterior tibial already described (five days), one is impressed with the slight degree

7. Ramón y Cajal (footnote 4, fig. 18).

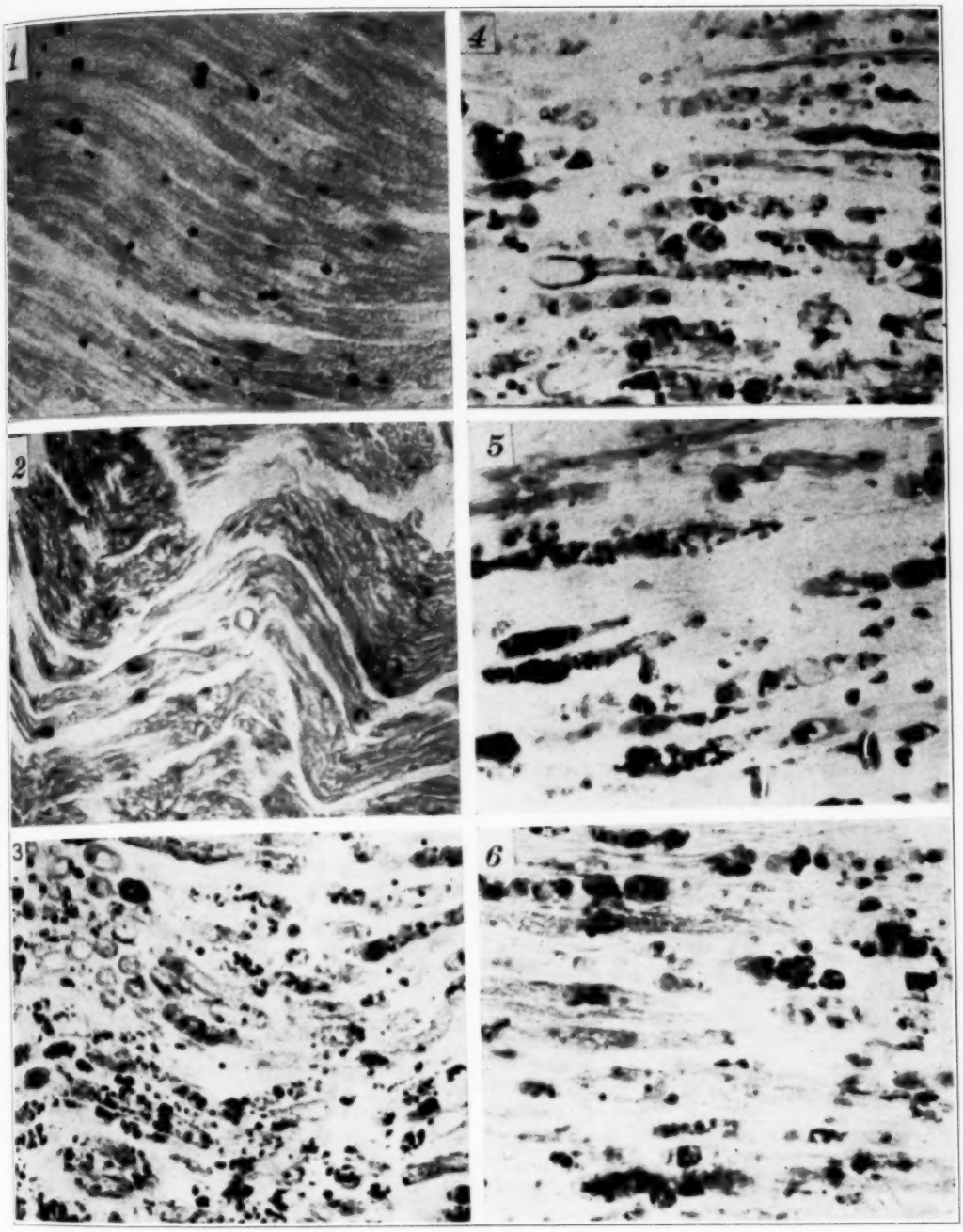

Fig. 2.—Peripheral nerves at successive stages following the onset of paralysis, prepared by the Marchi method. *1* shows the left sciatic nerve from a normal monkey; *2*, the left sciatic from the preparalytic stage also exemplifying the normal peripheral nerve picture. Compare with *3*, which shows the right sciatic nerve at nine days of paralysis; *4*, the left sciatic at eleven days of paralysis; *5*, the left radial at twenty-five days of paralysis, and *6*, the right sciatic at thirty-three days of paralysis. Zeiss 8 mm. Oc × 10, 275 diameters.

of damage in the present case. Protocols of the two monkeys gave evidence that the extent of paralysis was quite similar.

The right and left radial and right posterior tibial nerves of another monkey (no. 80), killed ten days after the onset of paralysis, were studied. In the right radial nerve approximately one fifth of the large, thickly myelinated fibers were found to be in the advanced stage of degeneration, but very few in the early stage. However, many medium-sized fibers were in early or moderately advanced stages. Fine, myelinated fibers were unaltered. Substantially the same distribution of degenerated fibers prevailed in the left radial. In the right posterior tibial, more than one third of the large fibers were in a moderately advanced state, only a few were in the early stage and the remainder were unaltered. Figure 1, *5* is a photomicrograph illustrating the distribution of degenerative changes in the right deep radial nerve of another monkey (no. 23) killed on the same day of paralysis and with changes almost identical with those described for this nerve.

Neurilemma cell proliferation was quite marked in degenerating fibers of affected nerves beginning at seven days following the onset of paralysis. Nerve segments fixed in formaldehyde-chrome-sublimate, mordanted in osmic acid for several days, sectioned after paraffin embedding, and stained with copper chrome hematoxylin showed frequent mitotic figures. One of these from the right radial nerve of monkey 80 (ten days of paralysis) is illustrated in figure 3, *1*.

In a monkey killed fourteen days following the onset of paralysis in the lower extremities, sections of the left posterior tibial showed more than one-third its large fibers to be in an advanced stage of degeneration. Medium-sized fibers were less frequently affected and the small variety were unaltered. Frequent mitotic figures were found in appropriately fixed material stained with copper chrome hematoxylin (fig. 3, *2*). They were more numerous than in the corresponding nerve from the tenth day of paralysis.

The right sciatic nerve of a monkey paralyzed for eighteen days (monkey 28) had infrequent normal large or medium-sized fibers, with the exception of a cluster of the latter, possibly sensory. The majority of the small, myelinated ones were normal. The majority of large, thickly myelinated fibers showed advanced degeneration, but a few appeared to have been rather recently affected; the degenerating medium-sized fibers had fragmented myelin (fig. 1, *7*).

In monkey 19, thirty-three days after the onset of paralysis in the upper extremities, the right radial nerve was selected for study. Its large fibers presented the final stage of degeneration (fig. 1, *8*). Many fine, myelinated fibers remained unaltered, but very few normal ones of medium and large size could be found.

Alterations in Myelin Sheaths Investigated by the Marchi Method: Study of peripheral nerves removed at intervals following the appearance of paralysis and subjected to the Marchi technic bears out the observations after osmic acid fixation already reported, as to both the size distribution of the affected fibers in poliomyelitis and the similarity of

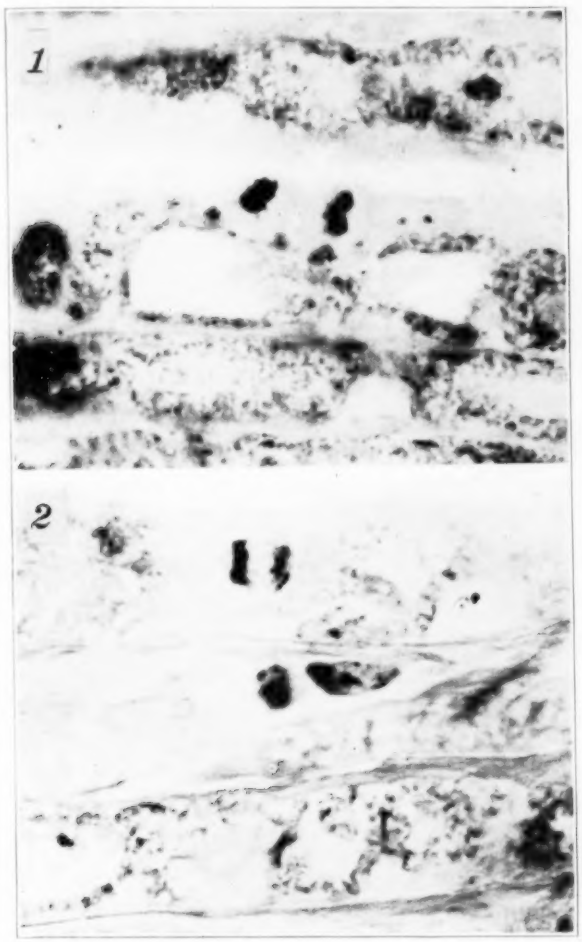

Fig. 3.—Mitotic figures in Schwann cells of degenerated peripheral nerve fibers, poliomyelitis. *1* shows the right posterior tibial (ten days). *2*, the left ulnar (fourteen days). Formaldehyde chrome sublimate, osmic acid mordanting, colored by copper chrome hematoxylin. Zeiss 2 mm. 1.3 Oc × 10, 1175 diameters.

the degenerative changes to those observed when peripheral nerves are severed from their cells of origin. Figure 2 illustrates the appearance of typical nerves from the ninth (fig. 2, *3*), eleventh (fig. 2, *4*), twenty-fifth (fig. 2, *5*) and thirty-third (fig. 2, *6*) days of paralysis as com-

pared with a section of normal monkey nerve (fig. 2, *1*) and one from the preparalytic stage (fig. 2, *2*).

Myelin Sheath Degeneration in the Phrenic Nerve Investigated by the Osmic Acid Method: Figure 4 permits the comparison of phrenic nerves from two monkeys that died on the seventh (no. 22) and tenth (no. 23) days of paralysis from respiratory impairment, with a phrenic nerve from a normal monkey, and one from a monkey (no. 59) that died on the tenth day, but exhibited no evidence of respiratory impairment until death. Early and moderately advanced degenerative changes were obvious in the majority of fibers of the phrenic nerves of the two monkeys that died following respiratory impairment (fig. 4, *2* and *4*), whereas the phrenic nerve of the monkey that died following ten days

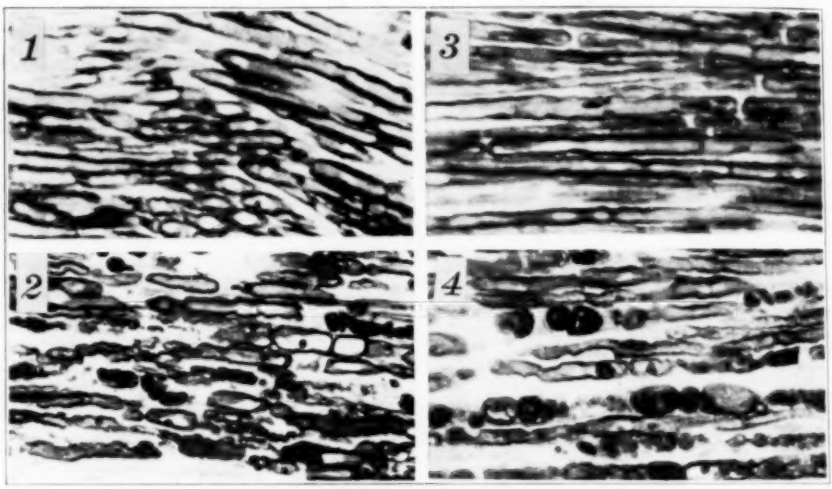

Fig. 4.—Phrenic nerves; osmic acid fixation. *1* and *3*, respectively, are taken from a normal monkey and from one that died after eleven days of paralysis, during which time it had suffered no severe respiratory discomfort. Compare the normal appearing myelin sheaths with the moderately advanced degeneration apparent in *2* (seven days) and *4* (ten days), monkeys that died following a period of respiratory discomfiture. Zeiss 8 mm. Oc × 10, 275 diameters.

of paralysis without obvious respiratory impairment appeared quite normal (fig. 4, *3*). The degree of depression of the action potential coincided with the histologic findings.

Axonal Changes in Peripheral Nerve Fibers Studied by the Cajal-Ranson Silver Method.—Study of the axons of nerves removed at various stages following the onset of paralysis indicates that there is no microscopically visible difference in the character of the axonal lesion which results from destruction of the anterior horn cells in poliomyelitis from that following section of a peripheral nerve. After four days

of paralysis, a large proportion of the axons of the left radial nerve (monkey 62) remained apparently normal. Not uncommonly, however, somewhat varicose axons were found which might be interpreted as evidence of a very slight stage of degeneration. Varicose axons were observed quite frequently at six days of paralysis, and there can be no doubt at this stage that these represent actual degenerative changes, since all transitions were found at successively later stages between these and completely dissociated axons.

Degeneration in the Sacral Spinal Roots.—Since the virus of poliomyelitis usually affects most severely the motor neurons, the presence of many normal fibers in a mixed nerve is to be expected, though it complicates the interpretation. Study of nerve roots permits a closer correlation between loss of function and pathologic change. It is to be noted, however, that not all efferent neurons innervate skeletal muscle, and nothing is assured regarding the selectivity of the virus of poliomyelitis for those that do. Because we found some ventral roots of affected segments in the late stage of our series (ten to twenty days) with no normal appearing fibers except certain of the fine, myelinated ones, and since the degree of anatomic change as a whole corresponded pretty closely with the degree of functional loss (oscillograph records), it is our belief that any or all anterior horn cells may be affected irrespective of their terminal connections.

The osmic acid preparations of sacral roots, corresponding to branches of the lumbosacral plexus studied, were examined at stages of paralysis from four and one-half to twenty days (fig. 5). The changes in the motor root fibers were the same as in fibers of mixed nerves, except for the proportion of the total number affected. After five days of paralysis, a majority of the fibers in motor roots corresponding to cord segments with widespread lesions showed moderately advanced changes, the number increasing with time until all fibers might become affected. Degeneration involving the majority of fibers in a sensory root was an exceptional occurrence. We found but one instance of it in our entire series, a sacral sensory root of monkey 57, eleven days (fig. 5, *3*). In the roots of all other monkeys studied, only occasional sensory fibers were found to be degenerating.

FUNCTIONAL STUDIES

Experiments carried out on monkeys at various intervals after the appearance of paralysis were designed to determine the site of first functional loss. A group of paralyzed muscles was selected for observation. Under light ether anesthesia, the spinal cord above the segments the cells of which innervated the muscles themselves was stimulated with a

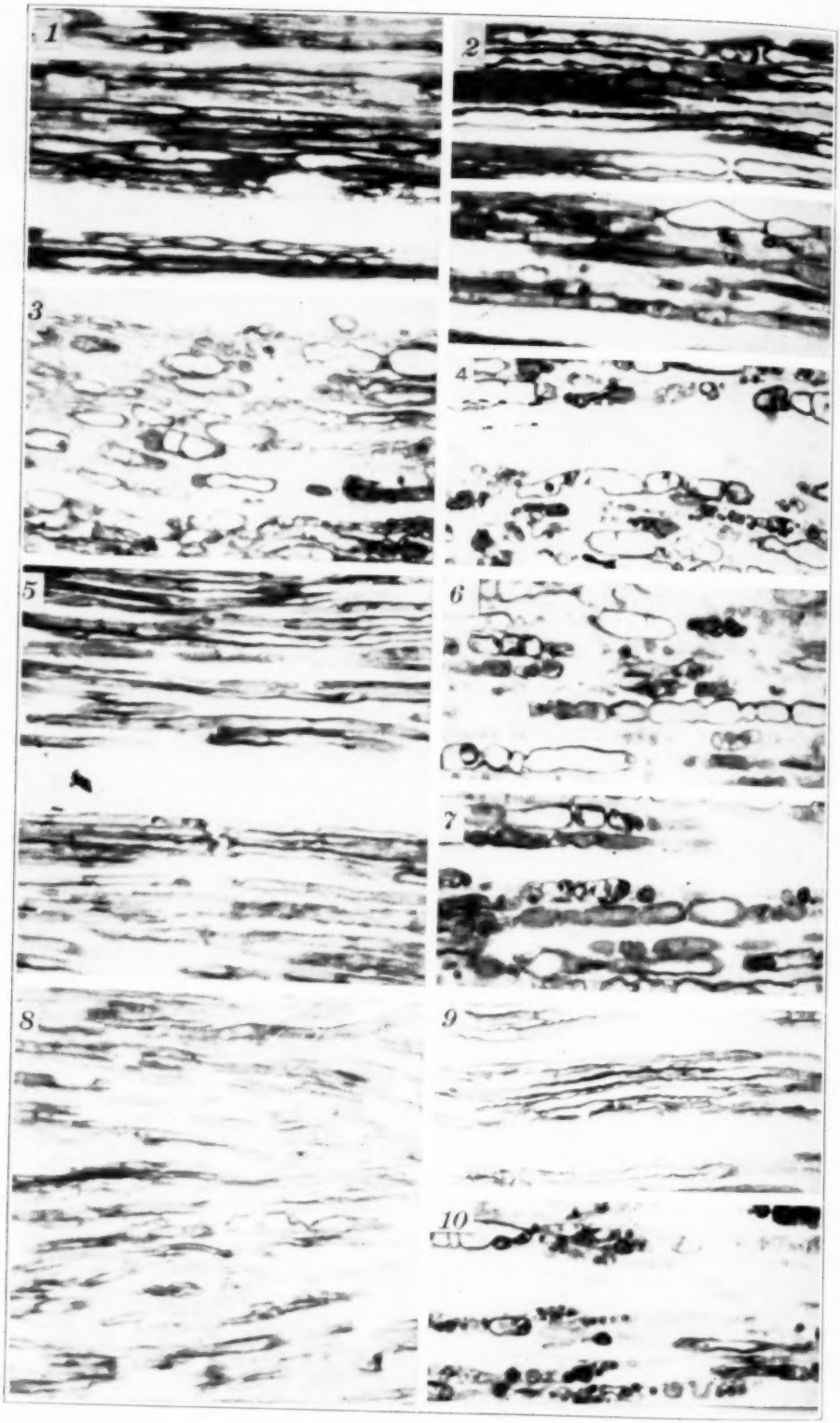

Figure 5

EXPLANATION OF FIGURE 5

Fig. 5.—Several spinal roots of monkeys killed in successive stages following the onset of paralysis; osmic acid fixation. *1* and *2* are sacral roots of normal monkeys; *2a*, the right sacral motor root (four and one-half days of paralysis) showing moderately advanced degenerative changes in approximately one-half its fibers; *3*, the sensory left sacral root (eleven days), with advanced degenerative changes in a majority of its fibers (this is the exceptional finding in the roots of paralyzed monkeys); *4*, the motor sacral root corresponding to the aforementioned sensory and in the same stage of degeneration; *5*, an unaltered sensory root (ten days). Compare with *7*, the corresponding motor root, all fibers of which show advanced degenerative change. *6* shows the sacral motor root (nine days), with advanced degenerative changes; *8*, the right sensory sacral root with sporadic fibers in a moderately advanced stage of degeneration. Compare with *10*, the motor root of the same segment, from which no action current could be elicited, and *9*, a motor root from an adjacent unaffected segment which has a good action current. Zeiss 8 mm. Oc × 10, 275 diameters.

galvanic current. In specially selected cases it was found that during the first two or three days of paralysis there was complete absence of muscle response on stimulation of the cord above the level of the cells innervating the muscles under observation. At this time response in the same group of muscles to stimulation of the proper motor roots and peripheral nerves was still good. Later, from four to ten days after the onset of paralysis, varying somewhat with the case, the muscular response to root and nerve stimulation was perceptibly weakened and in still later stages often entirely absent. Even at this time, direct stimulation of the muscle always resulted in contraction. These experiments demonstrated the site of first functional loss to be in the nerve cell or at its synapse with the upper motor neuron.

With the same materials utilized in the aforementioned experiments, attempts were made to determine any possible differences in the degree of degeneration existent in the axons at different sites along their courses. This was considered important in relation to the problem of the manner of progression of the virus along nerve fibers. If the spread of virus is out from the cord, it might be expected that degeneration would be first apparent and most marked in early stages in the regions near the cord. The results of galvanic stimulation and the oscillographic records of the action potential did not reveal any evidence to indicate that degeneration was not uniform throughout the length of the axon in the region of the peripheral nerve. These changes are similar to those seen by us in the study of degenerative processes in normal axons separated from their cells of origin. From a comparison of histologic sections of peripheral nerves and corresponding roots, it would appear that degeneration proceeds with more rapidity in the roots. The explanation of this difference may lie in observations of some investigators that when root fibers are severed, they degenerate more rapidly than those of peripheral nerves.

Experiments to compare the degree of functional alteration in sensory and motor roots were performed by recording their conducted action potentials with the cathode-ray oscillograph. The normal potentials recorded from sensory and motor roots of the monkey were first studied. It was then possible to compare the potentials of motor and sensory roots corresponding to cord segments the cells of which were injured by the virus and to gain an impression of the deviations from the normal. The accompanying table gives significant physiologic data concerning the state of the fibers in affected nerves and roots at various stages of the paralysis.

The marked involvement of motor roots of affected segments compared with corresponding sensory ones was definitely revealed by the discovery of significant differences in the series of recorded potentials

(fig. 6). It can be said, in general, that there was relatively little involvement of the sensory roots studied as indicated by the slight diminution in the area of the recorded potential. Usually, however, there were some increase in the absolute refractory period of the slower sensory fibers and lessening of their conduction rate. In but one sensory root (monkey 57, eleven days paralysis) was the fiber impairment marked. Since this was the only one removed from this animal for examination, it is not possible to state how widespread the sensory involvement was. In motor roots, on the other hand, definite diminution in area of recorded potential was found as early as the fourth day after the appearance of paralysis. This increased with the duration of paralysis, so that it was not uncommon to find an absence of action current in a motor root after ten to fourteen days. However, even in those motor roots of the late stage most severely affected, as indicated functionally by marked lessening of the total area of recorded potential, some fibers retained an approximation of their normal conduction rate. The functional results narrated were borne out by study of osmic acid-stained sections of the roots. In addition, Dr. W. P. Covell, working under the same grant and in close cooperation with us, studied histologically the segments of the cord from which these motor roots arose (article V of this series). He found uniformly that in the later stages of paralysis (from seven to fifteen days) loss of the action currents was correlated with severe damage or total destruction of the anterior horn cells.

It was not possible to record accurately the potentials from more than three roots in the same animal, because the physiologic properties of roots are altered more rapidly than those of peripheral nerves following removal from the body. However, successful results showed that in some cases adjoining roots on the same side, or right and left belonging to the same segment, differed significantly in function. In one, the action potential might not be appreciably affected, and in another it might be entirely absent. These results checked closely with Dr. Covell's findings in the cord, and with the appearance of the fibers in osmic acid preparations of the roots themselves.

It is important to note that the potential components elicited from the sensory roots, with properties indicating their origin from fibers similar to the fine, myelinated ones of autonomic nerves (Heinbecker [8] and Bishop and Heinbecker [9]), were still well developed at a time when depression of the potentials recorded from the motor roots was complete. On the other hand, potentials elicited from motor roots, with a

8. Heinbecker, P.: The Potential Analysis of the Turtle and Cat Sympathetic and Vagus Nerve Trunks, Am. J. Physiol. **93**:284, 1930.

9. Bishop, G. H., and Heinbecker, P.: Differentiation of Axon Types in Visceral Nerves by Means of the Potential Record, Am. J. Physiol. **94**:170, 1930.

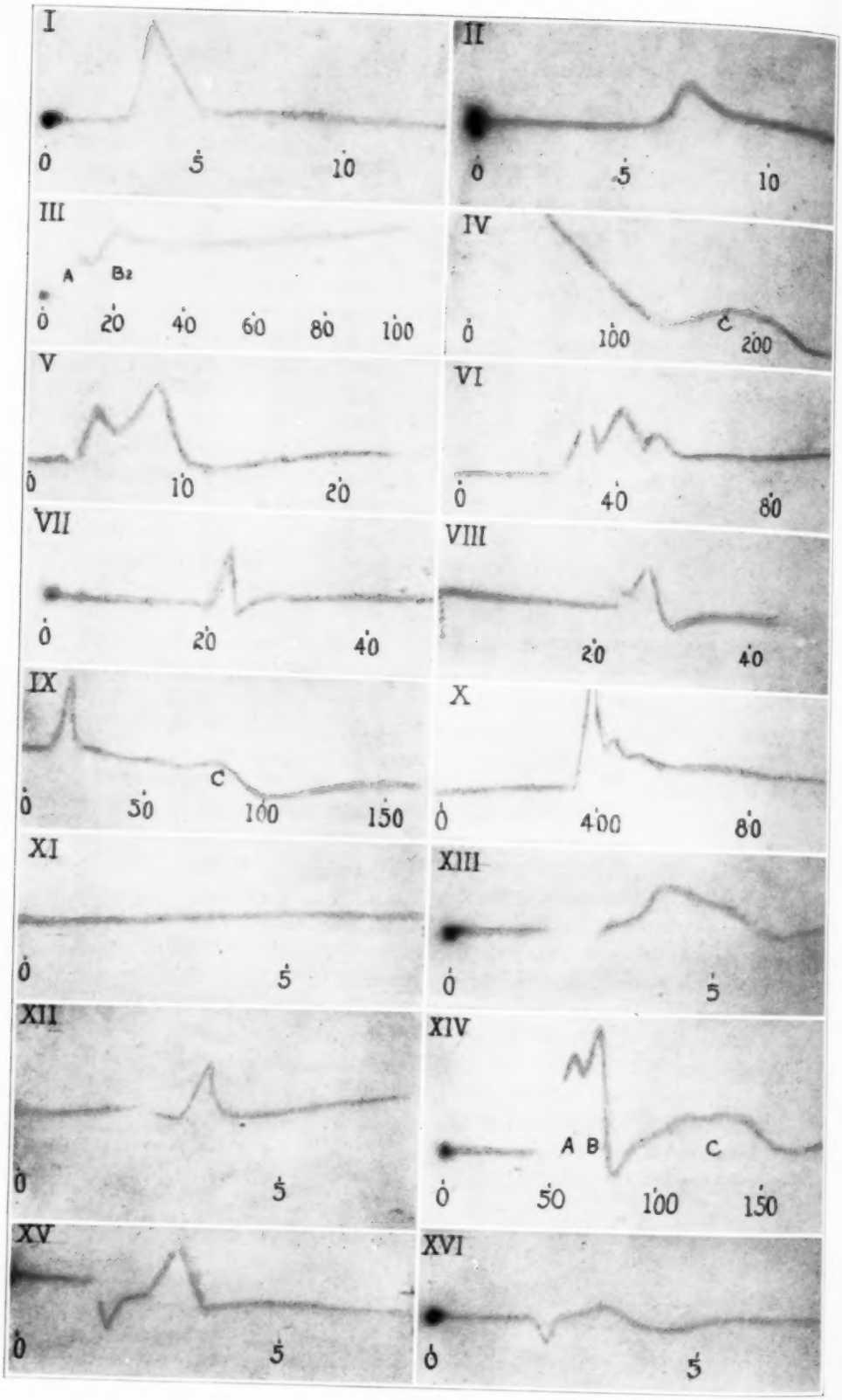
I
0
5
10
II
0
5
10
III
A
B2
0
20
40
60
80
100
IV
0
100
C
200
V
0
10
20
VI
0
40
80
VII
0
20
40
VIII
20
40
IX
C
0
50
100
150
X
0
400
80
XI
0
5
XIII
0
5
XII
0
5
XIV
A B
C
0
50
100
150
XV
0
5
XVI
0
5

Figure 6

EXPLANATION OF FIGURE 6

Fig. 6.—*I*, conducted action potential through the sacral sensory root; temperature, 36 C.; conduction distance, 22 mm. Time is marked in sigmas in this and all subsequent records; amplification, 10 mm. per millivolt. Paralysis was of five days' duration. *II*, conducted action potential of the corresponding motor root; temperature, 36 C.; conduction distance, 22 mm.; amplification, 10 mm. per millivolt. *III*, same preparation as for *II*, but amplification 180 mm. per millivolt. The first, or *A*, component is beyond the limits of the tube and a low, late potential ($'B_2$) is seen. No *C* potential is present. Histologically, there is no evidence of unmyelinated fibers in the cross-section of this motor root. *IV*, same preparation as for *I*, but amplification 180 mm. per millivolt. Note the well-developed *C* potential. Osmic acid cross-sections of this root reveal many unmyelinated fibers. *V*, conducted action potential through the sacral motor root; temperature, 37 C.; conduction distance, 25 mm.; amplification, 180 mm. per millivolt; paralysis, seven days. *VI*, conducted action potential of corresponding sensory root; temperature, 37 C.; conduction distance, 30 mm.; amplification, 180 mm. per millivolt. The first, or *A*, potential, extends beyond limits of the tube. It does not show well on the record. *VII*, conducted action potential of the sacral motor root from the same monkey as preparation *VI*; temperature, 37 C.; conduction distance, 27 mm.; amplification, 180 mm. per millivolt. *VIII*, conducted action potential of the corresponding sensory root; temperature, 37 C.; conduction distance, 29 mm.; amplification, 10 mm. per millivolt. The action potential amplitude is, therefore, about ten times as great in the sensory as in the motor root. In the normal, they are of comparable order of magnitude. *IX*, same preparation as for *VIII*, but with amplification 180 mm. per millivolt. Note the well developed *C* potential derived from unmyelinated fibers. *X*, conducted action potential of posterior tibial nerve of above monkey; amplification, 180 mm. per millivolt. *A* wave beyond limits of tube. A well developed action potential may obtain in a mixed nerve where the motor components are much reduced. To get significant data, examination of the roots is essential. *XI*, conducted action potential of sacral motor root; temperature, 37 C.; monkey paralyzed eleven days. At the amplification employed, 10 mm. per millivolt, no "wave" is discernible. *XII*, conducted action potential of the same preparation as for *XI*, with amplification 180 mm. per millivolt. *XIII*, conducted action potential of the sacral sensory root corresponding to preparation for *XI*; temperature, 37 C.; amplification, 10 mm. per millivolt. *XIV*, conducted action potential of the posterior tibial nerve; paralyzed eleven days; temperature, 37 C.; amplification, 180 mm. per millivolt; conduction distance, 32 mm. *XV*, conducted action potential of the sacral motor root of the same monkey as *XIV*; temperature, 37 C.; amplification, 180 mm. per millivolt. *XVI*, conducted action potential of the sacral sensory root corresponding to preparation for *XV*; temperature, 37 C.; amplification, 10 mm. per millivolt.

threshold and conduction rate similar to those ordinarily characteristic of autonomic fibers, were often depressed along with the potentials derived essentially from the large somatic motor fibers. The difference in the area of the two components in the motor root is so great that it is inadvisable to hazard any statement in regard to the order of their depression. It is possible, however, to say definitely that potentials with properties similar to those of visceral fibers were ordinarily depressed in affected motor roots.

Certain more irritable fibers in the sensory and motor roots and nerves were prone to have conduction rates faster than those found in the normal animal, especially early in paralysis. Their absolute refractory periods were likewise often shorter than normal. These observations would indicate a hyperactivity of the processes or materials involved in nerve function, like that artificially induced by an increase in temperature.

The interpretation of potential records (fig. 6) from mixed nerves in experimental poliomyelitis is not without difficulties. Even when paralysis has been long existent, the threshold, conduction rate and absolute refractory period values (table) may show little change, or even be found altered in a positive direction; these values are, of course, always for the most irritable or least depressed axons. The most useful criterion, particularly in the later stages of our series, was the change in total area of potential as compared with the normal. Such comparisons could be most precisely made close to the point of stimulation, and with amplification adequate only to record the potential of the somatic motor and sensory fibers. Since even complete loss of function in the motor fibers may occur with the sensory fibers normal (see root studies), an action potential of one-half the amplitude of the normal, for example, from the nerve trunk as a whole, may indicate complete loss of motor fiber response—a condition to be determined precisely only by study of the nerve roots.

Summarizing, then, the results of physiologic studies in general terms, we may say that for a considerable time after the appearance of paralysis (from four to ten days) many fibers are capable of conducting an approximately normal nerve impulse, though the cells of origin are functionally unresponsive. The loss of conduction through the nerve cells seems to reach the maximum earlier, and also more frequently, than loss of conduction in peripheral fibers, even though allowance is made for the time required for the disappearance of the action potential in normal fibers severed from their cells of origin (from two to four days). Consequently, it seems evident that many damaged cell bodies in poliomyelitis exert a favorable trophic influence over their fibers after their conducting function has disappeared. That such damaged cells

may die even as late as ten days after the onset of paralysis is made evident by the histologic observation of actively degenerating fibers in affected nerves of monkeys killed at this and later stages. Undoubtedly some of these cells may also recover, for in many cases of human poliomyelitis varying degrees of restoration of function occur.

COMMENT

An examination of the literature fails to reveal any complete studies on the nature of degenerative changes in spinal roots and peripheral nerves in poliomyelitis. Investigators have concentrated their efforts more on the intraspinal lesions occurring in the disease, influenced in this, no doubt, by the work of Redlich [10] and of Mönckeberg,[11] who showed conclusively that degeneration in peripheral nerve fibers was secondary to injury of their cells of origin.

Redlich applied the osmic method to the study of typical peripheral nerves and spinal roots of a female child, 5 months of age, who died about six days after the appearance of paralysis. He observed the degeneration of isolated fibers in the right recurrent laryngeal, "hochgrädige" degeneration in both phrenic nerves, and widespread changes in the left fourth cervical roots and in the right radial nerve. Mönckeberg studied, by the Weigert method, typical nerves of another child, 12 years of age, who died ten days after the onset of paralysis in the lower extremities. In the anterior roots of the affected segments he found fibers in all stages of degeneration, but in the posterior roots of the same segments, none.

Gowers,[12] while discussing a case of poliomyelitis that came to autopsy several years after recovery, stated that the anterior roots of the most affected segments of the cord were small and gray, and that degenerated motor fibers might be traced down the nerve trunks. Robertson and Chesley,[13] using the Marchi method, demonstrated that patchy degeneration of fibers in both anterior roots and peripheral nerves occurred early in the course of the disease.

Batten [14] reported cell infiltration of the peripheral nerves during the acute stages, but stated that it is with difficulty that such infiltration may be said to produce either the symptoms or pathologic results.

10. Redlich, E.: Beitrag zur pathologischen Anatomie der Poliomyelitis anterior acuta infantum, Wien. klin. Wchnschr. **7**:287, 1894.

11. Mönckelberg, J. G.: Anatomischer Befund eines Falles von Landryschen Symptomenkomplex, München. med. Wchnschr. **50**:1958, 1903.

12. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston's Son & Co., 1907.

13. Robertson, H. E., and Chesley, A. J.: Pathology and Bacteriology of Acute Anterior Poliomyelitis, Arch. Int. Med. **6**:233 (Sept.) 1910.

14. Batten, F. E.: Acute Poliomyelitis, Brain **22**:115, 1916.

Physiologic Data on State of Fibers at Various Stages of Paralysis

Preparation	Day After Onset of Paralysis	Temp. of Nerve, C.	Thresholds (Voltage and Capacity)				Rates (Meters per Second)				Absolute Refractory Period (Sigma)				Comment
			A	B_1	B_2	C	A	B_1	B_2	C	A	B_1	B_2	C	
Monkey 41	..	....	.....	.....	.....	.....	....	....	...	...	....	...	...	...	$C_1 = 0.001$; $C_2 = 0.005$; $C_3 = 0.01$; C_4 0.1 mf.
Left deep femoral.....	0	37.0	1.5 C_2	4.5 C_2	45 C_2	135 C_2	36.0	12.5	5.1	0.5	1.0	...	...	...	Potential fatigues readily
Left femoral.....	Prepara-	37.0	1.5 C_1	3.0 C_1	16.5 C_1	32 C_1	32.5	11.0	6.0	0.5	0.8	...	...	...	
Left phrenic.....	lytic stage	39.0	3.0 C_1	9.0 C_1	?	?	40.0	13.6	...	...	....	...	...	..	B_2 and C potentials present but of low amplitude
Left sciatic.....		37.5	1.5 C_2	.....	.....	.....	....	....	...	...	....	...	...	...	
Sacral spinal ganglion		39.0	.....	.....	.....	.....	....	....	...	...	....	...	...	...	Low action potential through ganglion; fatigued readily
Sacral spinal ganglion		38.0	.....	.....	.....	.....	....	....	...	...	....	...	...	...	Medium-sized action potential through ganglion; well sustained
Monkey 62	4														
Left deep femoral.....		37.0	1.5 C_1	16.5 C_1	15 C_4	22 C_4	34.0	16.4	2.4	0.8	0.93	1.0	...	...	Early histologic changes
Right sciatic.....		37.0	3.0—C_1	?	?	14 C_4	39.0	?	?	0.6	1.20	...	...	...	B_1 and B_2 components indefinite
Right radial.....		38.0	3.0—C_1	?	7.5 C_4	90 C_4	38.0	?	9.0	?	1.20	...	...	...	B_1 component indefinite
Left radial.....		38.0	1.5—C_1	.....	.....	.....	30.0	?	...	...	....	...	...	...	All waves present but only A measured
Monkey 84	4.5														
Sacral sensory root....		37.0	.....	.....	.....	.....	40.0	....	...	...	....	...	...	...	Sensory root shows few degenerating fibers
Sacral motor root.....		37.0	.....	.....	.....	.....	20.0	....	...	...	....	...	...	...	Motor root shows moderate number of fibers degenerating
Monkey 22	7														
Saphenous.....		38.0	3.0 C_1	15 C_1	36 C_1	22 C_4	26.8	9.4	?	0.5	....	...	...	...	Little histologic evidence of degeneration
Left phrenic.....		38.0	4.5 C_1	16.5 C_1	30 C_1	37 C_4	31.8	17.5	3.8	0.5	....	...	...	...	Considerable histologic evidence of degeneration (fig. 3, 2)
Genitofemoral.....		38.0	1.5 C_1	6.0 C_1	?	106 C_1	26.4	13.5	?	0.3	....	...	...	...	All waves depressed in amplitude
Deep femoral.....		38.0	3.0 C_1	23 C_1	10.5 C_4	30 C_4	27.0	6.6	0.8	0.3	....	...	...	...	Degeneration marked
Right ulnar.....		38.0	3.0 C_1	.....	.....	.....	40.0	....	...	...	....	...	...	...	All waves present but depressed for amplitude and readily fatigued
Monkey 66	7														
Right radial.....		37.0	4.5 C_1	22 C_1	?	80 C_4	29.0	9.0	?	0.4	0.82	1.0	...	...	
Genitofemoral.....		37.0	1.5 C_1	10.5 C_1	22 C_1	30 C_4	28.9	8.8	5.0	0.3	0.7	0.8	...	...	All waves present, further data not secured
Left radial.....		35.0	3.0 C_1	.....	.....	.....	27.5	....	...	...	....	...	...	...	
Right sciatic.....		37.5	1.5 C_1	6.0 C_1	33 C_3	105 C_4	30.0	11.5	1.5	0.5	....	...	...	...	
Left femoral.....		37.0	1.5 C_1	16.5 C_1	6 C_4	25 C_4	25.0	10.5	5.5	0.4	0.8	...	...	...	C wave fatigued readily

Monkey 59	9														
Right vagus		38.0	4.5 C_1	15 C_1	60 C_1	67 C_1	30.0	7.5	6.0	0.6	0.67	...	...	5.0	
Left sciatic		38.0	1.5 C_1	9.0 C_1	90 C_1	90 C_1	36.0	13.0	4.6	0.8	0.73	...	...	...	Amplitude high
Right sciatic		37.8	3.0 C_1	9.0 C_1	38 C_1	67 C_1	30.0	12.0	0.7	0.5	1.0	...	...	...	A amplitude depressed
Right radial		38.0	4.5 C_1	?	157 C_1	90 C_1	27.0	12.0	9.0	0.3	1.2	...	...	...	A amplitude at 3 panels = 2 mm.
Left radial		37.0	1.5 C_1	9.0 C_1	45 C_1	90 C_1	33.0	13.5	5.6	0.4	0.8	...	...	...	A amplitude at 3 panels = 7 mm.
Monkey 80	14														
Sacral sensory root		37.0	3.0 C_1	.....	.....	.....	39.0	....	...	...	....	...	...	...	Other waves present, data not recorded
Sacral motor root		37.0	9.0 C_1	.....	.....	.....	9.0	....	...	...	....	...	...	...	No C wave present
Monkey 28	18														
Lower cervical	18	37.0	1.5 C_1	6 C_1	45 C_1	22 C_1	28.0	11.0	3.5	0.5	....	...	...	...	B_2 and C potentials easily fatigued
Phrenic		37.0	.....	.....	.....	.....	....	....	...	...	....	...	...	...	No action potential elicited; histologic evidence of degeneration marked
Radial		37.0	.....	.....	.....	.....	....	....	...	...	....	...	...	...	A wave of low amplitude, no other potential elicited; marked degeneration
Monkey 26	20														
Sacral spinal ganglion		37.5	.....	.....	.....	.....	...	.. .	...	...	....	...	...	...	All waves elicited through ganglion, amplitude high, nearly normal; histologic section shows few degenerating fibers
Sacral spinal ganglion		37.5	.....	.....	.....	.....	....	....	...	...	....	...	...	...	All waves elicited through ganglion, amplitude approximately ½ normal; changes in more than one half the fibers
Sacral spinal ganglion		37.5	.....	.....	.....	.....	....	....	...	...	....	...	...	...	All waves elicited through ganglion, amplitude low
Right femoral		37.5	.....	.....	.....	.....	....	....	...	...	....	...	...	...	All waves elicited and of good amplitude
Monkey 19	33														
Right radial		37.0	9 C_2	16.5 C_2	67 C_2	Abs.	40.0	17.4	6.0	...	1.4	...	...	...	Action potential depressed and easily fatigued
Right femoral		37.0	4.5 C_1	16.5 C_1	Abs.	Abs.	27.0	9.0	...	...	0.9	...	...	...	Radial nerve shows advanced degeneration in many fibers; femoral nerve shows moderate degree of degeneration

Study of the peripheral nerves by the Marchi method showed the usual degeneration of efferent fibers; but with Weigert-Pal staining he proved that a considerable number of normal fibers remained. Larkin[15] reported degeneration of the myelin sheaths of peripheral nerve fibers in human cases during the acute stage, as indicated by the fragmentation of the myelin into cylinders and globules. Blanton,[16] in the same year, found degenerative changes in the peripheral nerves in one of four cases in which nerves were fixed at autopsy in osmic acid. This patient died thirty-six hours after the onset of paralysis, too early, he thought, for degenerative changes to manifest themselves as a result of ventral horn destruction.

Recently, Hurst,[17] referring to a monkey killed thirty-five days after the appearance of paralysis, commented on the degeneration of medullated fibers in the anterior roots and typical peripheral nerves. He stated: "The right median nerve stained by the Weigert-Pal method showed no absolutely normal myelin sheaths. . . . Some of the sheaths and axons had entirely disappeared leaving only a mass of proliferated Schwann cells along their course." Kopits[18] has also published recently an extensive critical review and the findings in seven cases in which bits of affected muscles were removed during orthopedic operations on persons several years after recovery from the acute stage of poliomyelitis. The small nerve fibers in the affected muscles were studied, and, in addition, he investigated the N. tibialis, N. peroneus and N. peroneus superior of a man who died twenty years after the acute stage of paralysis. In these nerves he observed atrophy of the myelin sheaths and varicosity of the axis cylinders, but solution of continuity only in the case of relatively few fibers.

In attempting to follow the changes consecutively in both histologic structure and physiologic response of affected nerves in monkey poliomyelitis, the greatest difficulty has been met in evaluating the changes of one type in terms of those of the other. This is much more difficult than in the case of cut nerves, for there all axons are in approximately the same stage of alteration at the same time, while in poliomyelitis not all the cells are affected to a like degree at once. It is, therefore, neces-

15. Larkin, J. H.: Macroscopic and Microscopic Findings in Poliomyelitis, Arch. Pediat. **34**:601, 1917.

16. Blanton, W. B.: An Anatomical Study of Fifteen Cases of Acute Poliomyelitis, J. M. Research **36**:1, 1917.

17. Hurst, E. W.: The Histology of Experimental Poliomyelitis, J. Path. & Bact. **32**:457, 1929.

18. Kopits, I.: Beiträge zur Muskelpathologie. Histologische Befunde an Muskeln, Nerven und Blutgefässen in Spät und Endstadien peripheralen Lähmungen, mit besonderer Berücksichtigung der Poliomyelitis anterior acuta, Arch. f. Orthop. **27**:277, 1929.

sary to take into account the threshold value for these changes, that is, the least change that can be observed by either technic.

In general, motor paralysis definitely precedes any noticeable change in the axons in poliomyelitis; that is, the cells (or synapses) are blocked before histologic changes in the fibers appear. The difficulty is to determine how many cells must be affected before paralysis is detectable, in the presence of many other as yet unaffected cells, and how many fibers must be injured before action potentials from the whole trunk appreciably decrease. Histologically, on the other hand, a change in a single fiber can be accurately observed even if all the other fibers are normal. The histologic technic, then, tends to emphasize the most affected fibers, while the functional studies supply a measure of the state of the most normal fibers, since these are the most irritable; and so far as they do more than this, they tend to give an average of normal and affected fibers. This is a fair measure in cut nerves, but not when the fibers vary in condition among themselves in the same nerve. Relative amplitude with respect to the normal has been the most reliable index to fiber depression, and this is not the most sensitive of criteria, and does not differentiate between absence of potential in a few fibers and decrease in amplitude of potential in many. The correlation between the findings of the two technics should not, therefore, be so exact in poliomyelitis, but the more abrupt the death of the affected cells, the closer these results should approximate to those from cut nerves in preciseness, since the more nearly coincident the involvement of the cells the more nearly alike is the condition to that which obtains in normal severed nerves.

From other investigators we know that nerve depressants may affect differentially the physiologic properties used here as a measure of nerve function. Some agents, like cocaine, appear to alter primarily the refractory period, which is an index of irritability and fatigability, without much effect on the intensity of response as indicated by the amplitude of the action potential. Other agents (and these include nerve poisons such as aconitine, behaving more like toxins) decrease the intensity of response in each fiber considerably before the fiber fails to respond. The tests necessary to establish differences in mode of action by any agent require that only one region of the axon be affected, so that the normal activity may be measured beyond this region, in normal nerve, for comparison with the depressed portion. If the amplitude of potential decreases in the depressed region, but is normal beyond, we know that it has been depressed in each fiber, to recover in the normal segment farther on, while if the amplitude decreases in both regions, we know that some fibers have failed to conduct. This very specific criterion cannot be applied either in nerves degenerating in

poliomyelitis, or in the cut nerves we have used for comparison with these, for apparently in both these cases the fiber is affected throughout its length, and not locally.

However, in general, a fiber that can be stimulated locally will conduct; and conduction fails with many depressants when the threshold to electrical stimulation has increased from two to three times, and when the refractory period has about trebled. In cut nerves, when the degenerative process is started in all fibers at once, lowering of amplitude takes place before the thresholds and refractory periods have increased this much, and this we take to be an indication that the nerve's response is depressed in intensity gradually in all the fibers before conduction fails, rather than suddenly in each of successive fibers. These conclusions, on the inference that the cause of fiber depression is primarily loss of function of the cell, should hold also in poliomyelitis.

Recent studies concerned with the transport of the neurotrophic viruses along peripheral nerves have emphasized the importance of the axis cylinders in the passage. Since no evidence has been adduced to the contrary, it may be assumed that if such transport occurs, it does so with equal facility in either direction. In the case of poliomyelitis, Nicolau and Galloway [19] have shown that the virus moves peripherally along nerve trunks, Fairbrother and Hurst,[20] that it migrates in a central direction. Goodpasture,[21] in his study of the virus of herpes, has reached the conclusion that its passage within the axon is a process of growth. This is indeed the only logical interpretation of his observation; for passive transport would allow opportunity for adsorption on the axon surfaces which would result in depletion of the already minute quantity that we can conceive of as gaining access at the site of peripheral injury to the fibers. One would expect that active growth within the axons should produce an altered physiologic response in the nerve fibers much earlier than that which is due to cell injury. The fact that a longer time usually elapses after cell block before the first signs of fiber degeneration than elapses between the cutting off of the cell body and a similar degeneration of the fiber, suggests that the virus itself is not the direct cause of the fiber injury. Furthermore, there is no evidence that the myoneural junction is affected before fiber degeneration, a situation that might be expected if the virus acted periph-

19. Nicolau, S.; Dimancesco-Nicolau, Mme. O., and Galloway, I. A.: Étude sur les septinévrites à ultravirus neurotropes, Ann. Inst. Pasteur **43**:1, 1929.

20. Fairbrother, R. W., and Hurst, E. W.: The Pathogenesis of, and Propagation of the Virus in, Experimental Poliomyelitis, J. Path. & Bact. **33**:17, 1930.

21. Goodpasture, E. W.: The Axis-Cylinders of Peripheral Nerves as Portals of Entry to the Central Nervous System for the Virus of Herpes Simplex in Experimentally Infected Rabbits, Am. J. Path. **1**:11, 1925.

erally, since this region is more susceptible to the action of some agents, such as curare and strychnine, than is the nerve. In one respect, however, we have found evidence to indicate that a difference exists between the changes occurring in fibers corresponding to affected segments of the cord in poliomyelitis and the course of degeneration following nerve section. In several monkeys killed during the preparalytic stage and first days of paralysis, the threshold of the large somatic fibers in nerves and roots belonging to affected cord segments was lowered and their refractory period shortened, that is, nerve irritability was increased. This change, absent in the stages of degeneration of severed normal nerves, can bear two interpretations: direct injury of the axons by growth of the virus within them, or a reflection in the axons of the effect of its growth within the cell.

In the experiments conducted to demonstrate the efficiency of the axon in the transport of viruses, peripheral injury of fibers has been a necessary accompaniment. It is well known that damage in the course of a nerve fiber causes characteristic changes in the cell body, its nucleus, apparatus of Golgi and Nissl substance. These morphologic alterations may be, and probably are, accompanied by decrease in the resistance of the cell to injurious agents, so that they might be expected to respond more quickly to a virus which had gained access to them by whatever route than their unaltered fellows.

Hurst [22] interprets the results of recent experiments as very favorable to the view of axon transmission. Following intrasciatic inoculation of the virus of poliomyelitis, the cord cells earliest affected were those the fibers of which course in the sciatic, and, except for concentric spread, the lesions next appeared in the cortical motor area corresponding to the sciatic nerve into which injection had been made. However, the possibility that the virus in its passage through nerve tissue follows the line of least resistance along fiber bundles, instead of within the substance of the axons, remains to be disposed of.

SUMMARY

Peripheral nerves and spinal roots from the affected cord segments of thirty monkeys killed at intervals subsequent to the appearance of paralysis, were studied by physiologic and histologic methods. The changes were compared with those that occur following the severing of typical normal peripheral nerves, and also with the extent and severity of the lesions within the cord (Dr. W. P. Covell).

In poliomyelitis, conduction through the diseased anterior horn cells ceases before changes in the motor roots and peripheral nerves become

22. Hurst, E. W.: A Further Contribution to the Pathogenesis of Experimental Poliomyelitis: Inoculation into the Sciatic Nerve, J. Path. & Bact. **33**:1133, 1930.

apparent. In general, this period is significantly longer than that which elapses before changes are manifest in nerve trunks severed from their cells of origin. It varies with the degree of immediate cell destruction produced by the virus.

In only one respect have physiologic changes unlike those found in severed peripheral nerves been observed in the affected trunks. The discovery of increase in conduction rate and of shorter refractory periods indicates an increase in irritability of fibers during the preparalytic stage and the first days of paralysis. The bearing of this evidence on the theory of axonal transmission of virus is discussed.

The action potential of the small, myelinated (visceral) fibers of the motor roots of diseased segments is depressed along with that of the large, myelinated variety.

Pronounced sensory changes are the exceptional finding following intracerebral inoculation, although histologic evidence of degeneration is to be found in all roots studied. The fibers degenerating may be so infrequent that depression in the action potential of sensory roots cannot be detected.

The accompanying table gives significant physiologic data concerning the state of the fibers in affected nerves and roots at various stages of the paralysis.

DIAGNOSIS OF INTRACRANIAL TUMORS BY SUPRAVITAL TECHNIC

FURTHER STUDIES

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The routine use of the supravital technic in the diagnosis of intracranial tumors has led to greater proficiency in differentiating lesions at the time of operation, and the surgeon has come to depend more and more on its aid. During the period of about four years since the adoption of the method in Dr. Cushing's clinic, increased familiarity with the true microscopic appearances of the various forms of growth has gradually been acquired. The principles of the technic have already been described.[1] A number of cases reported in more or less detail may best serve to illustrate the further progress made. The following have been selected because of their possible interest, not only to the surgeon, particularly in those instances in which an immediate histologic diagnosis was essential to the conduct of the operation, but to the pathologist because of the peculiar and enlightening appearances of the tumors in supravital preparations as contrasted with fixed or sectioned specimens.

REPORT OF CASES

CASE 1 (P.B.B.H. surg. no. 36114).—*Atypical cerebellopontile syndrome; suboccipital exploration; exposure of cystic tumor with gross appearances of fibrillary astrocytoma; supravital examination: acoustic tumor; radical excavation.*

On March 27, 1930, Louis H., an iron-worker, aged 29, was admitted to the hospital with the complaint of headaches and unsteadiness. He had been deaf on the left side for about nine years, and on questioning gave a history of tinnitus of six months' duration. For eighteen months he had had severe frontal headaches, latterly associated with soreness of the neck. His gait became unsteady, with a tendency to fall to the left, and for ten months increasing attacks of dizziness occurred. For two months he had been aware of blurring of vision and numbness of the left side of the face.

On entrance, examination disclosed: bilateral choked disks of 5 diopters, advanced to blindness; loss of sensation over the left trigeminal area; left abducens palsy; left facial weakness; left deafness and positive Bárány test; ataxia, which was most marked in the left leg; positive Romberg sign, and diminished deep reflexes on the left.

From the Surgical Clinic of Dr. Harvey Cushing, Peter Bent Brigham Hospital.

1. Eisenhardt, Louise, and Cushing, Harvey: Am. J. Path. **6**:541, 1930.

On April 3, a suboccipital exploration was performed. The cerebellar hemispheres were bulging, the left being pushed to the right. A small amount of yellow fluid was evacuated from the left lateral recess, and a huge tumor occupying the outer part of the left cerebellar fossa and resembling a fibrillary astrocytoma was exposed. A portion extirpated for immediate examination by supravital technic was reported as neurinoma. Radical excavation with freeing of the growth from the ninth, tenth and eleventh nerves was made, the major portion of its posterior wall being removed.

The patient made an excellent recovery, though there was not much change in vision, and on discharge, April 26, was up and walking about. In a recent letter, Dec. 13, 1931, apart from impaired vision and occasional headache, he is reported to be free from discomfort.

Supravital Examination.—A typical neurinoma was found composed of interlacing bands and whorls of dense fibrillary tissue with spindle-shaped cells in palisade arrangement. The nuclei were generally elongated, containing fine chromatin particles and a small nucleolus. Numerous foam cells were present.

Comment.—Ordinarily there is no question in the clinical diagnosis of an acoustic tumor, and the histologic examination of the tissue is of interest chiefly to the pathologist, but in such instances as this it is of particular value to the surgeon at the time of operation.

Although there had been hesitancy on the part of one examiner in making a preoperative diagnosis of acoustic tumor because no history of preliminary tinnitus was elicited, the operator himself felt no uncertainty since the patient, having paid no attention whatever to his left-sided deafness, might well enough have forgotten a preceding tinnitus after an interval of eight or nine years. When, however, early during the operation a small amount of yellow cystic fluid was secured, the surgeon began to suspect that after all he would find a gliomatous cyst, and the lesion subsequently exposed was so large and so fibrous that it had all the appearances of a fibrillary astrocytoma filling the outer side of the posterior fossa and presumably extending to the fourth ventricle, one or two such cases having been previously encountered. The supravital examination, however, proved that the tumor was a neurinoma.

The appearances of an acoustic tumor in a supravital preparation are quite characteristic, as may be seen from figure 1 *A*. These tumors are commonly so firm that it is difficult to demonstrate isolated cells, but in figure 1 *B*, a photomicrograph of a single cell from another and softer growth recently removed is shown with all its processes intact. Such detail of cytoplasm and processes as seen here is hardly apparent in fixed preparations of acoustic tumors stained by ordinary methods.

CASE 2 (P.B.B.H. surg. no. 30627).—*Choked disks without localizing signs; subtemporal decompression; subsequent cerebellar syndrome; suboccipital explorations; final verification of tumor by supravital examination of débris from lumbar puncture needle following dry tap; roentgen therapy.*

Selmour R., a grocer, aged 35, was admitted to the hospital on June 5, 1930. He had always enjoyed good health until three months previously, when the onset of frequent attacks of severe headache, nausea and vomiting occurred, occasionally associated with stiff neck. There was also slight blurring of vision. He did not consult a physician until a month later, when he complained of pain in the back, epigastrium and lower extremities and loss of weight. Studies of the gallbladder, kidneys and gastro-intestinal tract gave negative results. He was referred from one clinic to another, finally entering the hospital.

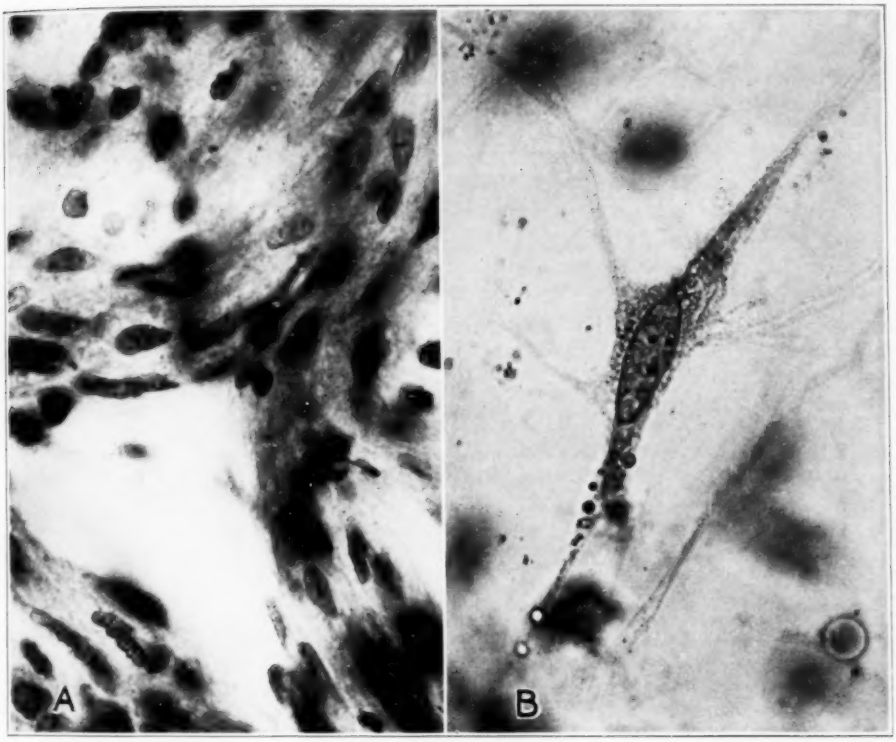

Fig. 1.—*A* (case 1), supravital preparation of an acoustic tumor, showing palisade arrangement of cells in bands of fibrillary tissue; × 600. *B* (P.B.B.H. Surg. no. 37160), supravital preparation of an acoutic tumor, showing an isolated cell with elongated nucleus, finely granular cytoplasm and stellate processes; × 850.

On examination he was found to have bilateral choked disks of 3 diopters and slight impairment of the olfactory sense on the left. Roentgenograms disclosed sacroiliac arthritis.

On June 26, following ventriculograms which indicated a posterior fossa block, a subtemporal decompression was made. The patient was discharged on July 12, quite relieved from symptoms apart from stiffness of the legs.

He rapidly became progressively worse, however; the pressure symptoms recurred, and he was readmitted in a bedridden condition on July 26. The objective findings were: bilateral choked disks of 2 diopters; ataxia, most marked in the right

arm and leg; diminished deep reflexes on the right, and retropulsion. While being prepared for operation he had a cerebellar seizure with temporary loss of consciousness.

On July 29, a suboccipital exploration was performed. The cerebellar hemispheres appeared normal, but on splitting the dura in the midline a white nodule, as big as a pea, was disclosed on the posterior surface of the medulla. Owing to respiratory embarrassment, no tissue was removed for identification.

Postoperative roentgen therapy was given, but the patient failed to make satisfactory progress. He was greatly undernourished and presented a decubitus. It was decided to attempt removal of the tumor.

On September 4, a reexploration was made, with evacuation of a meningeal xanthochromic cyst. The vermis was transected and the dilated ventricle opened. On investigating the region in which the previous operator had disclosed a tumor, a cotton pledget plastered in the region of the foramen was found. It was adherent and was dislodged with difficulty. Tension having subsided, the wound was closed.

There was little change in the patient's condition following this procedure. He was incontinent and sometimes irrational. On the tenth day after the operation, the decompression being tense, a lumbar puncture was performed and xanthochromic fluid obtained.

On the eighteenth day, repeated lumbar punctures were attempted, but no fluid was secured. A puncture was then made by Dr. Cushing, also resulting in a dry tap, but on inserting the stylet he noticed some débris in the lumen and submitted it for immediate examination by supravital technic. A diagnosis of tumor was reported. Roentgen treatment was given to the whole spine. The patient was discharged to a nursing home on October 9.

He was readmitted on November 13 for a second course of roentgen therapy. By this time there was astonishing improvement. He entered the ward in a wheel-chair, was free from discomfort and normal mentally. The decubitus had healed.

On Jan. 5, 1931, he returned for another treatment. He had continued to improve and was able to walk a few steps without support. Soon after this, however, he began to fail, and death occurred on April 11, 1931.

Supravital Examination.—A minute fragment of soft tissue, less than the size of a pinhead, was removed from the lumen of a lumbar puncture needle. On examination it was seen to be composed of masses of cells, generally round in shape, with round or oval nuclei, though elongated and irregular forms were present. There was little intercellular tissue. Mitoses were numerous, from two to three being found in a single oil immersion field. Many phagocytic cells were present. The diagnostic impression was that the growth was a medulloblastoma.

Comment.—This is an instance of verification of tumor by immediate examination of tissue obtained in the lumen of a lumbar puncture needle and noticed by the surgeon on withdrawal after a dry tap.

With the meager objective findings on the patient's first admission, a diagnosis of "cerebellar tumor suspect" was made, and his abdominal and spinal discomforts were attributed to a sacro-iliac arthritis as evidenced in the roentgenogram. The rapid progression of a cerebellar syndrome, however, soon led to the assumption that a subtentorial lesion must be present. The suspicious nodule disclosed in the medulla at the primary operation was not removed owing to respiratory difficulties. At the

second exploration, carried out in the hope of verifying the lesion and excavating enough of the growth to relieve symptoms, it again was not feasible to remove any tissue. It was not until almost three weeks later that the presence of the growth was actually verified histologically following the dry lumbar tap.

The supravital technic is particularly well adapted to such an emergency in diagnosis; the amount of tissue was infinitesimal, it tended to dry rapidly, and there was consequently little time to be lost in examining it. Though the specimen was partly dried, the cellular detail

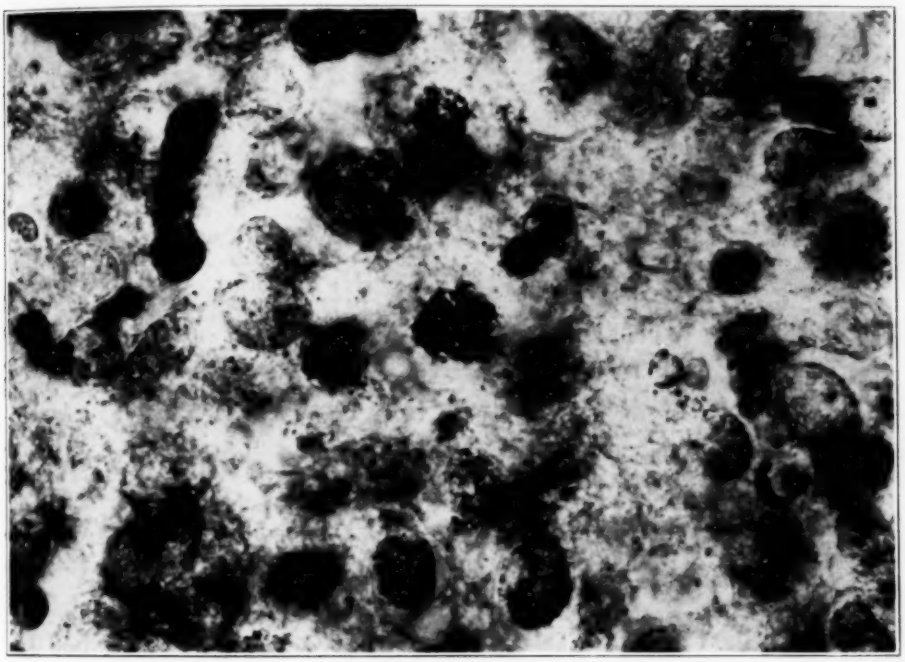

Fig. 2 (case 2).—Supravital preparation of débris from the lumbar puncture needle after a dry tap, verifying a suspected medulloblastoma. A mitotic figure is in the center of the field; × 850.

is fairly well shown in the photomicrograph (fig. 2). There was no doubt on microscopic study that this was a rapidly growing tumor, probably a medulloblastoma of the cerebellum with metastasis to the cord.

Case 3 (P.B.B.H. surg. no. 37462).—*Chiasmal syndrome; preoperative diagnoses: aneurysm; meningioma; calcified adenoma; osteoplastic exploration; extirpation of meningioma; confirmation of diagnosis by supravital technic.*

On Oct. 16, 1930, Mrs. Albertine E., a housewife, aged 56, was admitted to the hospital with the complaint of failing vision, which had been first noticed in August, 1929. At that time she consulted an oculist, who attributed the condition to high blood pressure. In spite of treatment by diet, rest and drugs, however,

her vision grew worse, and by January, 1930, she could no longer read ordinary newspaper print. In June, a reexamination of the eyes showed a fundus "suggestive of pituitary adenoma" and a bitemporal hemianopia. Pituitary tablets were prescribed, but vision continued to fail, and she was finally referred to the hospital. For nine months she had had occasional dizzy spells and had noticed a definite loss of memory. For two months there had been increasingly severe bitemporal headaches.

She was a cooperative patient, but slow in cerebration. The objective observations were: bilateral optic atrophy with marked loss of vision; bitemporal hemianopia; fine scanty hair, and delicate skin. The blood pressure was 210 systolic and 110 diastolic. The roentgenogram showed multiple areas of calcification within the pituitary fossa; the sella was not enlarged or deformed.

On Oct. 22, 1930, a right transfrontal exploration was made. There was excessive bleeding on elevating the flap. The dura was incised along the sphenoidal ridge, and on elevating the frontal lobe an unmistakable reddish granular meningioma to the left of the right optic nerve came into view. The vessels were nodular and atheromatous, the right anterior cerebral artery being twice its normal size. The growth was carefully dislodged and excavated, and the area of attachment to the sulcus chiasmatis was thoroughly coagulated.

The patient made an excellent recovery from the operation, with rapid improvement in vision. There were occasional complaints of pain in the left hip and leg, and the systolic blood pressure varied from 155 to 190. She was discharged to her home on November 22, with full vision and feeling well. On December 5, she died suddenly with the typical signs of a coronary embolus.

Supravital Examination.—The tissue was soft in consistency. It was composed of large fragile cells with oval and round nuclei. The delicate cytoplasm was distinctly outlined. The isolated cells were round but when in contact they assumed polygonal forms. There were a few whorls and psammoma bodies. The tumor was moderately vascular. The diagnostic impression was that the growth was a meningioma.

Comment.—This was an interesting case from the standpoint of differential clinical diagnosis. The long history of hypertension favored an aneurysm. As a matter of fact, at operation the blood vessels were found to be greatly diseased, and on reexamination of the roentgenograms it was concluded that the calcified areas noted were probably alongside of the sella as well as within it. The diagnosis of suprasellar meningioma was considered as the second possibility, for the patient was past middle age, with optic atrophy, bitemporal hemianopia and a small sella. Because of the multiple areas of calcification inside the pituitary fossa, the roentgenologist's impression was that the lesion was a calcified adenoma.

The gross appearance of the meningioma disclosed at operation was unmistakable. On microscopic examination of the supravital preparation, occasional early psammoma bodies were found, but the tissue was composed chiefly of large delicate cells, as shown in figure 3 *A*. It is interesting to compare this with the photomicrograph of the fixed preparation of the same tumor (fig. 3 *B*), for a considerable change

has taken place in the latter due to shrinkage, and the cytoplasmic outlines are no longer visible.

CASE 4 (P.B.B.H. surg. no. 37653).—*Astroblastoma of right central region; osteoplastic exploration; extirpation of cystic tumor; supravital examination: multinucleated giant cells.*

Doris L., aged 8, was admitted to the hospital on Nov. 17, 1930, with the complaint of morning vomiting, headaches and failing vision. The onset was sudden seven weeks previously, when the first attack of vomiting occurred. Frontal head-

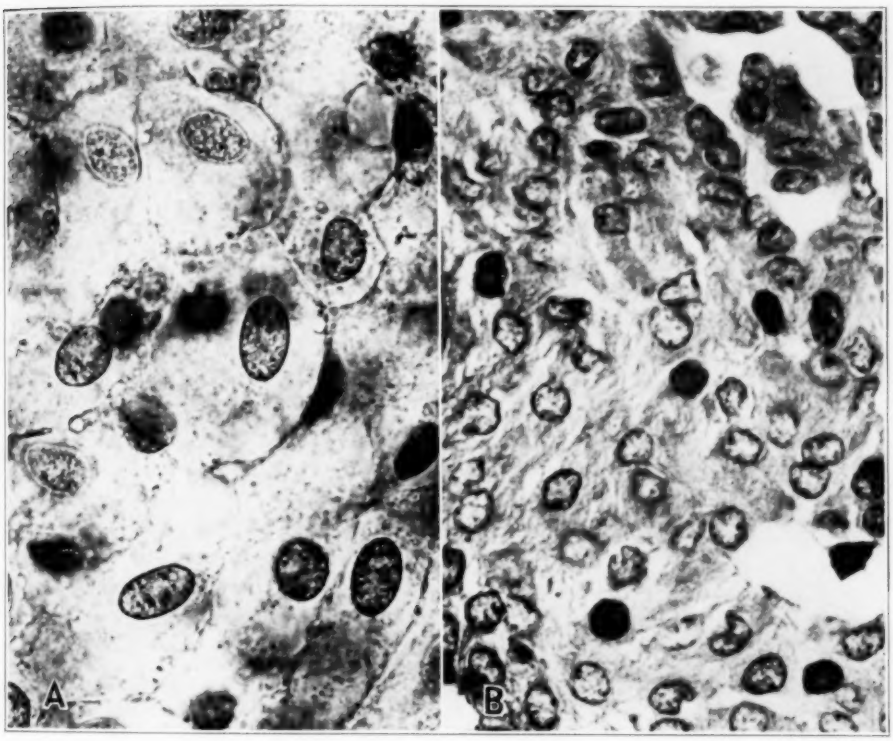

Fig. 3 (case 3).—*A*, supravital preparation of a meningioma. Note the large delicate cells with distinct cytoplasmic outlines; × 850. *B*, Zenker-fixed preparation of the same tumor as in *A* (eosin-methylene blue). The nuclei are shrunken; × 850.

aches, increasing in severity, had been present for about the same time. For six weeks her parents had noted dragging of the left foot, and the left arm became so weak that a cock-splint was applied. For three weeks the child had complained of failing vision and of seeing flashes of bright light.

On examination, visual acuity was found to be greatly diminished, with left homonymous hemianopia and bilateral choked disks of 3 diopters, advanced to optic atrophy. There were left facial weakness; left hemiparesis and hemihypes-

thesia; a positive Babinski sign, and absent abdominal reflexes on the left. The roentgenogram showed marked pressure atrophy of the skull.

On November 22, a right osteoplastic exploration was made, with reflection of a greatly thinned bone-flap and exposure of a central gliomatous tumor surrounded by a soft cystic area. The cyst was evacuated, and a firm mural nodule the size of a hen's egg extirpated.

The child made a prompt recovery, and on discharge, on December 10, the left-sided weakness was hardly perceptible. A letter dated Sept. 19, 1931, reported that she was in excellent health and planning to return to school.

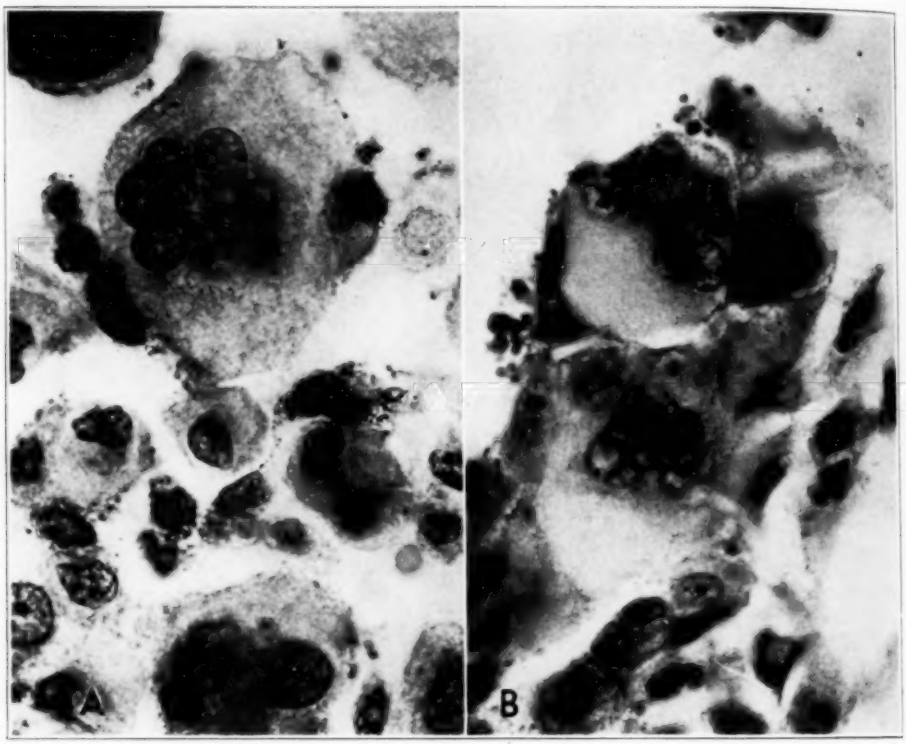

Fig. 4 (case 4).—*A*, supravital preparation of an astroblastoma to show multinucleated giant cells; × 850. *B*, Zenker-fixed preparation of the same tumor (eosin-methylene blue); × 850.

Supravital Examination.—The tissue was soft and easily "spread." The most prominent feature on examination by supravital technic was the presence of huge multinucleated cells throughout the preparation. These giant astrocytes were roundish in shape, had a finely granular cytoplasm and no processes, and contained clumps of from eight to ten nuclei. Other cells were uniform in size and had the appearance of astroblasts and astrocytes. They showed a perivascular arrangement. There was no evidence of rapid growth, and cells undergoing direct division were seen. The diagnostic impression was that the growth was an astroblastoma.

Comment.—At operation, the cyst with the large mural nodule was recognized as a benign type of glioma. The chief interest in this case lies in the microscopic appearance of the extraordinarily large multinucleated cells present in the tumor. For comparison with the supravital preparation (fig. 4 *A*), cells in the fixed preparation (fig. 4 *B*) with approximately the same number of nuclei were selected for photography, and while they have much the same general appearance there is a difference in size after fixation, as may be noted.

CASE 5 (P.B.B.H. surg. no. 37840).—*Osteoplastic exploration; extirpation of temporal lobe tumor with gross appearances of a glioblastoma multiforme; supravital diagnosis: spongioblastoma polare; final diagnosis: mixed type of glioma.*

On Dec. 15, 1930, Odiorne G., a retired postal carrier, aged 60, was referred from the Worcester City Hospital, where he had been admitted because of mental depression and epilepsy. For four years he had recurrent jacksonian sensory attacks beginning in the left leg and extending to the left arm, accompanied by twitching of the foot and hand. There was never loss of consciousness. He began to drop letters while distributing mail and to drag his foot. This increased to such an extent that he was obliged to quit work. For three years he had intermittent attacks of morning vomiting. A year before entrance, the onset of headaches occurred, and for six months, because of bumping into people, he had noticed impairment of vision on the left.

He was an elderly man, slow in response, and unable to stand or walk. Examination disclosed: choked disk of 2 diopters on the right; left homonymous hemianopia with split macula; unequal pupils, the left being larger; slight right exophthalmos, and absent left corneal reflex. There were slight left lower facial weakness and left middle ear deafness. The left hemiparesis was most marked in the leg, and the left hemihypesthesia most marked to heat and cold. There was astereognosis of the left hand. The deep reflexes were exaggerated on the left, and the abdominal reflexes were absent. A roentgenogram showed multiple areas of calcification in the right temporal lobe.

On December 22, a right osteoplastic exploration was made. On reflecting the dura the surface extension of a large glioma spreading over the parietal cortex was exposed. The tumor was extirpated by block dissection to its depth in the temporal lobe. It was quite soft and succulent. At the base of the cavity was a tough nonsuckable core of the growth, from which one isolated fragment was dislodged.

The patient made an excellent recovery. The choked disk subsided, but the hemianopia remained unchanged. Roentgen therapy was given. He gradually gained strength in the left arm and leg, and on discharge, Jan. 17, 1931, was able to walk a few steps. A recent letter, dated Dec. 8, 1931, reported that he has steadily improved.

Supravital Examination.—The tissue was grayish in appearance. On making the preparation it was found to be surprisingly firm in consistency. It was composed almost entirely of spongioblasts, most of which were bipolar in type. The nuclei were slim and elongated, containing a prominent nucleolus and a moderate amount of chromatin. The processes were long and straight, and formed a fibrillary network of considerable density. There was no evidence of rapid growth. The diagnostic impression was that the growth was a spongioblastoma polare.

Studies of the calcified piece removed later during the operation showed a predominance of oligoglia. The diagnosis was glioma of mixed type.

Comment.—From the size and succulent character of the tumor, it was expected by the surgeon that the growth might prove to be a glioblastoma multiforme, although grossly no necrotic areas were apparent. Supravital examination of this softer portion, however, revealed a typical picture of a polar spongioblastoma. To rule out the possibility of this being a collection of spongioblasts in a glioblastoma, additional preparations were made, all of which showed the same uniformity of structure and no evidence of malignancy. The small calcified fragment

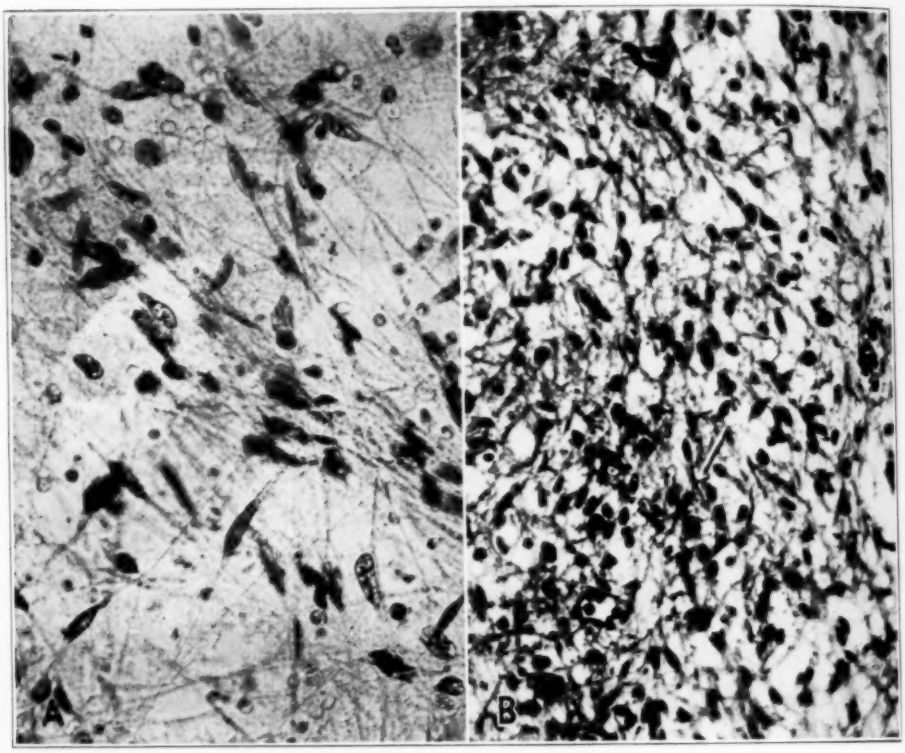

Fig. 5 (case 5).—*A*, supravital preparation of spongioblasts. The long wiry processes continue beyond the field; × 300. *B*, Zenker-fixed preparation of the same tumor (phosphotungstic-acid hematoxylin). The cells are shrunken. The arrow points to a unipolar spongioblast for comparison with *A*; × 300.

removed at the end of the operation was composed of oligoglia, so that the tumor represents a mixed type of glioma.

A photomicrograph of the spongioblasts in the supravital preparation (fig. 5 *A*) may be contrasted with that of a similar part of the tumor after fixation (fig. 5 *B*). The fresh preparation gives a much better idea of the extraordinary length of the processes of these cells

because they are not cut across as by the usual methods of sectioning. Even at this comparatively low magnification the shrinkage the cells have undergone after fixation is obvious.

CASE 6 (P.B.B.H. surg. no. 29787).—*Meningioma "en plaque" of right temporo-orbital region; osteoplastic exploration; extirpation of tumor; supravital examination of temporal muscle: diagnosis of invasion by tumor; removal of muscle.*

Mrs. Josephine P., a housewife, aged 55, was first admitted to the hospital on Oct. 4, 1927, with the complaint of prominence of the right eye for four years.

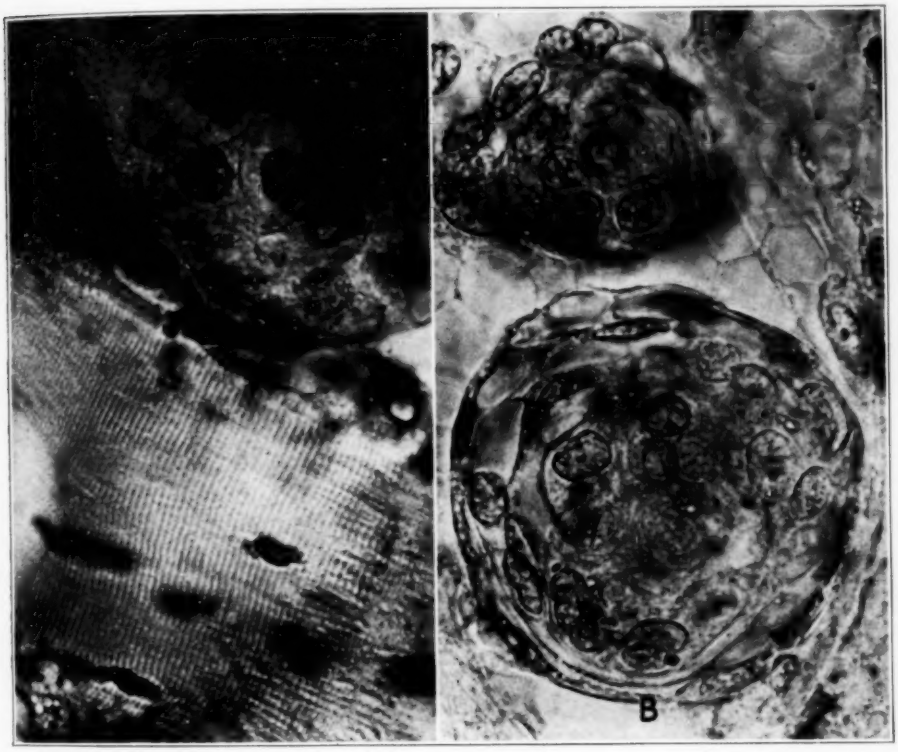

Fig. 6.—*A* (case 6), supravital preparation showing invasion of striated muscle by meningioma; × 850. *B* (P.B.B.H. surg. no. 28757), supravital preparation from the bone to show invasion by typical whorls of meningioma cells; × 850.

For some time before this, she had been aware of a fulness in the right temporal region. For two years there was tenderness on deep pressure or when chewing. Right-sided headaches had occurred, but had subsided during the last year.

Examination disclosed a bruit which was audible over the right temporal swelling. The roentgen findings were consistent with a meningioma of the right sphenoidal ridge. The patient was discharged without operation on October 15.

On Feb. 3, 1931, the patient was readmitted to the hospital. During the three year interval she had reported regularly for observation, and though there was no notable change in her condition, an operation was finally decided on.

A right osteoplastic exploration was made on February 10. The dura was vascular and adherent, and on breaking up the bone-flap there was excessive bleeding. A fragment of temporal muscle over the hyperostotic area of bone was submitted for immediate supravital study. This was found to be infiltrated by tumor. A layer of muscle was therefore removed. The thickened bone was pursued to the horizontal plane of the middle fossa, and a disk of dura containing a granular meningioma *en plaque* was extirpated.

The patient made a good recovery and was discharged on March 8, 1931, the exophthalmos having receded. A letter dated Dec. 15, 1931, reported that she is quite well.

Supravital Examination.—A small fragment of tissue was prepared in the usual manner. Examination showed that it was composed of striated muscle fibers invaded by typical meningioma cells.

Comment.—This case is included chiefly to demonstrate the possibility of making a supravital preparation of muscle. Although the histologic nature of the tumor was obvious to the operator, it was not certain to what extent the growth had involved adjacent tissues. It may be seen in figure 6 *A* how clearly the invasion of the striated muscle by tumor is shown in this type of preparation. The diagnosis was immediately reported to the surgeon, and the infiltrated layer of temporal muscle accordingly removed by electrosurgery.

Not only is it possible to study muscle by the supravital technic, but one may go even further and in certain cases apply it to the examination of bone. In a recent case of bilateral parasagittal meningioma *en plaque* with hyperostosis (P. B. B. H. surg. no. 28757), a secondary exploration was carried out owing to a recurrence of the growth after a three year interval. The edges of the old defect had undergone considerable new bone formation. On rongeuring the margin away in order to enlarge the opening, a fragment of bone from a suspicious area was submitted for examination. This was scraped with fine dissecting instruments, and the soft tissue and fluid thus obtained transferred to a slide and studied by supravital technic. In figure 6 *B*, a photomicrograph of the typical whorls of meningioma cells is shown. Here again the diagnosis of invasion by tumor was immediately reported to the surgeon, and the diseased bone was rongeured away to forestall possible extension or recurrence of the growth. It has proved very useful to examine bone in this way during operation in a number of cases.

CASE 7 (P.B.B.H. surg. no. 38288).—*Syndrome of frontal tumor; osteoplastic exploration; fragmentary removal of peculiar area in cortex; supravital examination: medulloblastoma; roentgen therapy.*

On Feb. 25, 1931, Ralph W., a clerk, aged 28, was admitted to the hospital. He had been in excellent health until two months before, when without warning a numbness of the right half of the tongue occurred. He tried to raise his right arm, and lost consciousness. Convulsions were observed by his fellow workers. He soon began to have from one to six attacks daily. When severe, they were

accompanied by twitching of the right side of the face, inability to talk and difficulty in swallowing. For six weeks there had been slight slurring of speech, a tendency to forget names and diminished vision in the right eye. For two weeks frontal headaches had been present.

On admission, he was up and walking about. The objective observations were: right lower facial weakness; early bilateral choking of disks; diminution of right corneal reflex, and very slight motor aphasia. These findings were regarded as sufficiently definite to justify operation without preliminary ventriculograms.

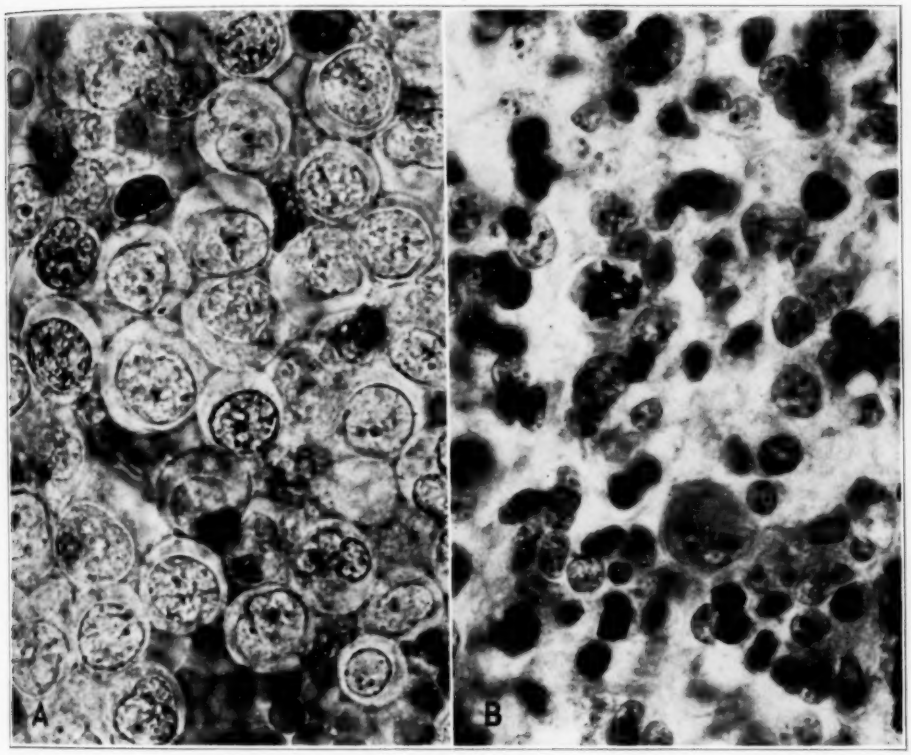

Fig. 7 (case 7).—*A*, supravital preparation of a medulloblastoma, showing clearly outlined cytoplasm and round shape of cells; × 850. *B*, Zenker-fixed preparation of the same tumor (eosin-methylene blue). The cytoplasm has lost its definition, and the nuclei are shrunken; × 850.

On March 7, a left osteoplastic exploration was performed, with exposure of flattened and bulging convolutions. In the region of Broca's convolution a peculiar area was incised, and a fragment removed for immediate examination. A diagnosis of medulloblastoma was reported. An attempt was made to pursue the lesion to a depth of 3 cm., but there was no demarcation of the tumor.

The patient made a good operative recovery. During the first week of convalescence several slight convulsions occurred. A series of roentgen treatments was given, and he was discharged on March 21. A letter reporting his death on June 30, 1931, was later received.

Supravital Examination.—The tissue was of soft consistency. Examination disclosed a cellular, rapidly growing tumor. The cells were round, with a small amount of clearly defined cytoplasm and a large nucleus containing abundant chromatin. Cells with two nuclei were present. Intercellular tissue was scanty. Mitoses were numerous. The diagnostic impression was that the growth was a medulloblastoma.

Comment.—The surgeon could not tell in this case whether the small surface area of peculiar appearance was cortex or tumor. After the

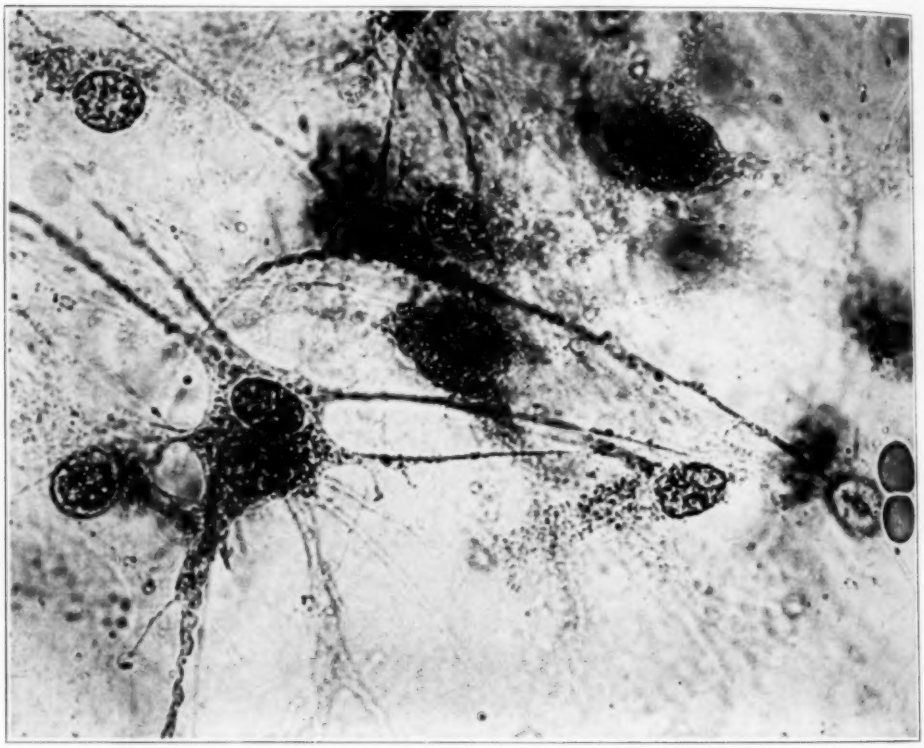

Fig. 8 (case 8).—Supravital preparation of a fibrillary astrocytoma, showing isolated cell with two nuclei and branching processes; × 850.

diagnosis of medulloblastoma had been made, the exploration was continued through the cortex, but the tissues were poorly demarcated and no further growth was apparent. In view of the fact that the supravital examination proved the tumor to be highly malignant, and, because of its dangerous location in the left hemisphere, further extirpation was considered inadvisable.

A photomicrograph of the supravital preparation is given in figure 7 *A*. The cytoplasm is intact, so that the round shape of the cells is

distinct. For comparison, a photomicrograph of the fixed preparation of the same tumor is shown in figure 7 *B*. Though it is a good tissue section and shows mitoses, the true form of the cells is lost, their delicate cytoplasm having been puckered by fixation. There is also a marked difference in the appearance of the nuclei in these two photomicrographs taken at the same magnification.

CASE 8 (P.B.B.H. surg. no. 39805).—*Cerebellar syndrome; suboccipital exploration; supravital examination: typical fibrillary astrocytoma.*

Esther S., a school girl, aged 16, was admitted to the hospital on Oct. 11, 1931. She had never had any previous serious illness. Two months before entrance she began to have dull morning headaches. A month later diplopia occurred, and a left internal squint was noted. An oculist prescribed glasses, but there was progressive failure of vision. She began to be troubled with dizziness. For three weeks she had been ataxic and confined to bed. She became increasingly fatigued and drowsy, lost appetite and weight, complained of noises in the left ear, and had attacks of morning vomiting.

On examination the objective findings were: choked disks, right 1 diopter, left 3 diopters; horizontal nystagmus, more marked to the right; left external rectus palsy; left facial weakness; diminished deep reflexes, and adiadokokinesia on the right. The gait was ataxic, and she was unable to stand in tandem position.

On October 17, a suboccipital exploration was performed, with disclosure of a laterally placed cystic astrocytoma. Total block extirpation of a mural nodule in the right hemisphere was made, with subsequent evacuation of a cyst extending to the midline, the fourth ventricle being widely exposed.

She made an excellent recovery, and was discharged free from symptoms on November 6.

Supravital Examination.—The tissue was composed of fibrillary astrocytes of typical stellate form. The nuclei were generally oval, containing a moderate amount of chromatin and one or two nucleoli. The cytoplasm was granular and the cells had many long branching fibrillae.

Comment.—This was a typical cerebellar syndrome pointing to a lesion on the right, and the tumor was at once recognized as a cystic astrocytoma when exposed at operation.

In figure 8, a cell with two nuclei is shown as it appeared in the supravital preparation. Though astrocytes may vary in their morphologic appearance, cells of star-shaped form are not at all an uncommon finding in these tumors. In this particular specimen they were plentiful, and any one of several preparations made might have been selected for photography.

If an astrocytoma is tough in consistency, one may find on microscopic examination that many of the cells are obscured by a heavy network of fibrillae. These fibrillae have a rather characteristic appearance in the fresh preparations (fig. 9 *A*). They are refractive and tend to be wavy. In this respect they differ from the processes of spongioblasts, which are remarkably straight and wiry looking (cf. fig. 5 *A*).

The appearance of giant astrocytes has already been referred to (cf. fig. 4 *A*).

The photomicrograph in figure 9 *B* of phagocytic cells found in an astrocytoma of the cerebellum is included merely as a matter of interest to demonstrate the particles of neutral red dye in the cytoplasm.

CASE 9 (P.B.B.H. surg. no. 40050).—*Chiasmal syndrome; preoperative diagnoses: aneurysm; meningioma; exposure of suprasellar nodule; supravital examination; identification of pituitary adenoma extruding through diaphragm; extirpation.*

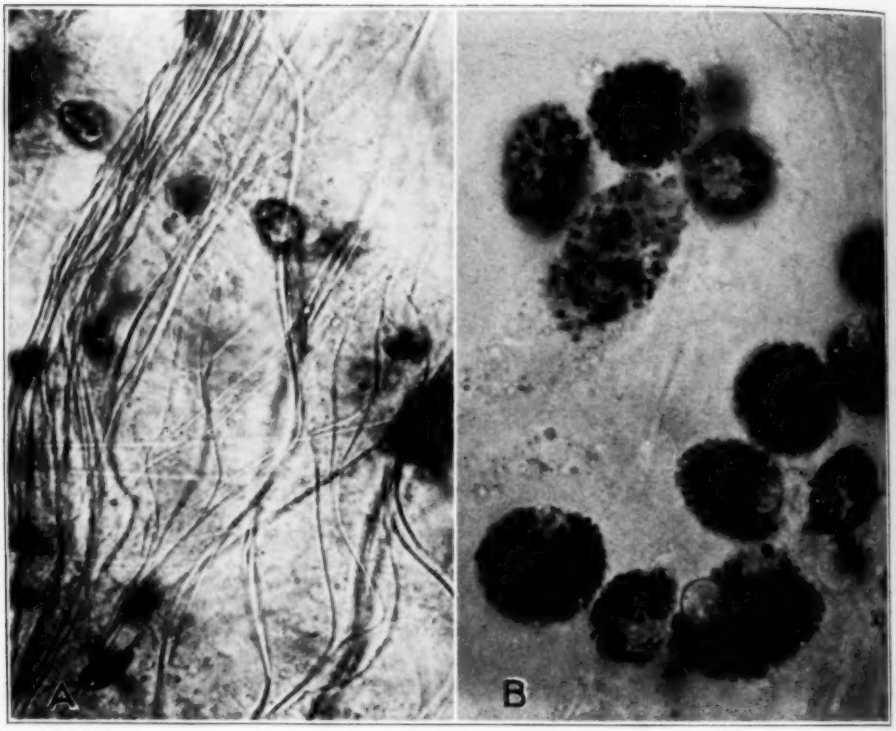

Fig. 9.—*A* (P.B.B.H. surg. no. 37307), supravital preparation to show the characteristic appearance of bands of fibrillae in an astrocytoma; × 850. *B* (P.B.B.H. surg. no. 37804), supravital preparation of phagocytic cells in an astrocytoma. Note the neutral red dye in the cytoplasm; × 850.

On Nov. 18, 1931, Miss Edith R., a graduate nurse, aged 59, was admitted to the hospital with the complaint of failing vision. Eight months before, while doing close work, she noticed that she could not see well. An ophthalmologist was consulted, who prescribed treatment for glaucoma. Vision continued to fail, however, and for six weeks she had had difficulty in seeing to the left.

On entrance she was found to have: low visual acuity, with left homonymous hemianopia; bilateral optic atrophy; soft silky hair, and fine skin. The roentgenogram showed depression of the left half of the pituitary fossa and signs of cerebral arteriosclerosis. During her stay of five days further constriction of the visual

fields occurred. An exploration was advised. The patient wished to go home first to attend to business affairs.

She returned on December 14, and three days later a right transfrontal exploration was made, with disclosure of a reddish glistening mass protruding to the left of the right optic nerve. It was tapped, but nothing was obtained. A few fragments were then removed for immediate microscopic examination. On receiving the diagnosis of adenoma, the surface nodule was excised and puckered by electrosurgery. An opening was then made into the dural diaphragm and a small adenoma scooped out. The nerves were entirely freed from pressure.

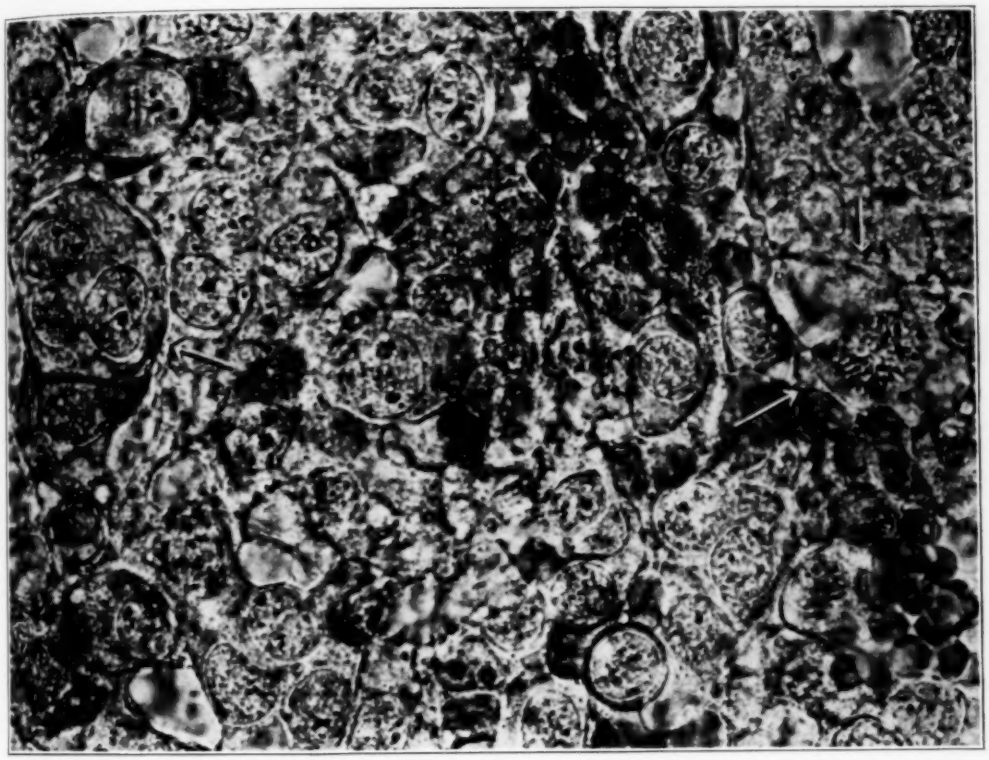

Fig. 10 (case 9).—Supravital preparation of a pituitary adenoma. Note the large cell with three nuclei to the left, and mitotic figure to right; × 850.

She made an excellent recovery and was up and about by December 27. The visual fields showed remarkable improvement, and there was a change in visual acuity from 20/30 on the right and 20/100 on the left before operation, to 20/25 in each eye after the operation. Roentgen therapy was begun, and she was discharged on Jan. 10, 1932.

Supravital Examination.—A fragment of tissue was examined and found to be fairly firm in consistency. On microscopic study, it was seen to be composed of masses of epithelial cells of varying size. The nuclei were oval or round, some containing large nucleoli. The cytoplasm was clearly defined, and here and there

were chromophile cells containing coarse alpha granules. Multinucleated cells were present, many of them large in size. Several mitotic figures were seen. The diagnostic impression was that the growth was pituitary adenoma of a mixed type.

Comment.—Though the patient presented a sufficiently definite chiasmal syndrome to justify a transfrontal exploration, there was considerable uncertainty as to the exact preoperative diagnosis. In view of her age and comparatively small sella, it was suspected that either an aneurysm or a suprasellar meningioma would be found. The left homonymous field defect was of a peculiar and irregular form and gave no clue to the type of lesion actually disclosed—a midline extrusion of an adenoma through the diaphragm sellae. This suprasellar extrusion had the gross appearance of either a cyst or an aneurysm. A tap being negative, a few fragments of the growth were removed for diagnosis by supravital technic. The lesion was immediately identified as an adenoma of mixed type (fugitive acromegaly), a photomicrograph of which is shown in figure 10. A mitosis happens to be included in the field as well as a large multinucleated cell. In view of the several mitoses observed in the supravital preparation, postoperative roentgen therapy was given.

CASE 10 (P.B.B.H. surg. no. 40185).—*Rapidly progressing hemiparesis; exploration; identification of glioblastoma multiforme by supravital technic; extirpation; fatality.*

On Dec. 11, 1931, John B., a merchant, aged 69, was admitted to the hospital with the complaint of weakness of the left side. For six weeks he had felt marked lassitude, and three weeks before entrance consulted a physician for the first time in his life. It was then noted that there were weakness of the left side and left hemihypesthesia, which gradually became worse. For two weeks he had been troubled with dizziness on looking upward or to either side. He remembered having had two or three dizzy spells in the last three years. He had become mentally depressed.

He was a robust, somewhat drowsy person. Examination disclosed: right anosmia; left homonymous hemianopia; lower left facial weakness; left pupil larger than the right; left hemiparesis, hemihypesthesia and astereognosis; hypoactive superficial and hyperactive deep reflexes on the left. The patient was left-handed.

On December 18, following preliminary ventriculograms, the patient became unconscious. A right central osteoplastic flap was at once turned down, and an exceedingly soft and full hemisphere with evident vascular changes disclosed. Multiple punctures gave negative results. The temporal lobe was incised and a fragment of tissue removed for immediate diagnosis. This proving to be tumor, the lobe was uncapped and a large degenerated growth containing an organized clot was radically extirpated by electrosurgery.

On the following day the patient became deeply stuporous. The flap was reelevated and a fair-sized clot removed. He failed to improve, however, and death occurred on December 20.

Supravital Examination.—The tissue was soft and on microscopic examination showed a rapidly growing glioma invading the brain. There was marked variation in size and type of cells, including astrocytes, spongioblasts and round cells without

processes. The nuclei were hyperchromatic, and lobated forms were common. There were numerous large multinucleated cells, some with seven or more nuclei, and an extraordinary number of mitoses. The diagnostic impression was that the growth was a glioblastoma multiforme.

Comment.—This patient was admitted with a questionable diagnosis, there having been a difference of opinion on the part of the physicians referring him. There was no elevation of the optic disks. The history of rapidly increasing left-sided paralysis was, however, apparently

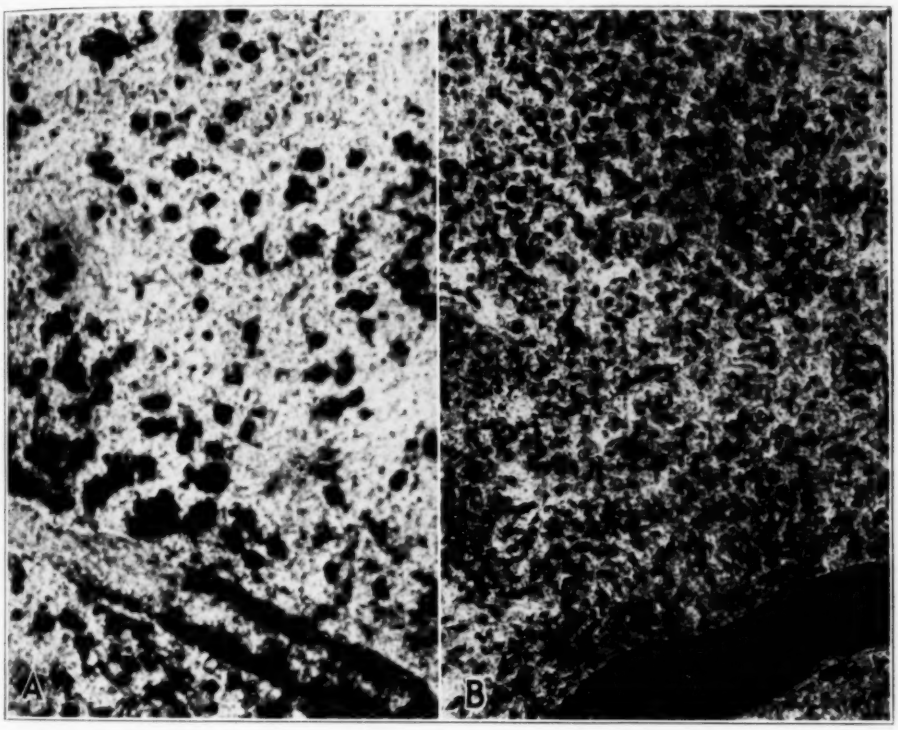

Fig. 11 (P.B.B.H. surg. no. 38085).—*A*, supravital preparation of a necrotic portion of a glioblastoma multiforme. Numerous phagocytic cells are in the neighborhood of the vessel; × 150. Compare with *B*. *B*, supravital preparation of viable tissue from the same tumor as in *A*. Such an area is preferable for diagnosis under higher magnification (cf. fig. 12); × 150.

definite. An emergency operation was carried out with the patient in coma after ventriculography. The organizing clot found in the center of the huge tumor probably accounted for the similarity of his syndrome to that of vascular disease. Though the outcome was unfavorable, the case illustrates another instance in which the supravital technic was of value in identifying the growth during the course of the

operation. The ventriculograms had indicated a deep temporal tumor, but multiple punctures into the soft brain yielded no information. When a fragment removed from the temporal lobe was reported as glioblastoma multiforme invading the brain, the lobe was uncapped and the main mass of growth exposed and removed.

The multiform glioblastomas, as is known, commonly undergo degenerative changes, and may be so necrotic that little in the way of viable tumor cells may be made out. A quick examination of the tissue

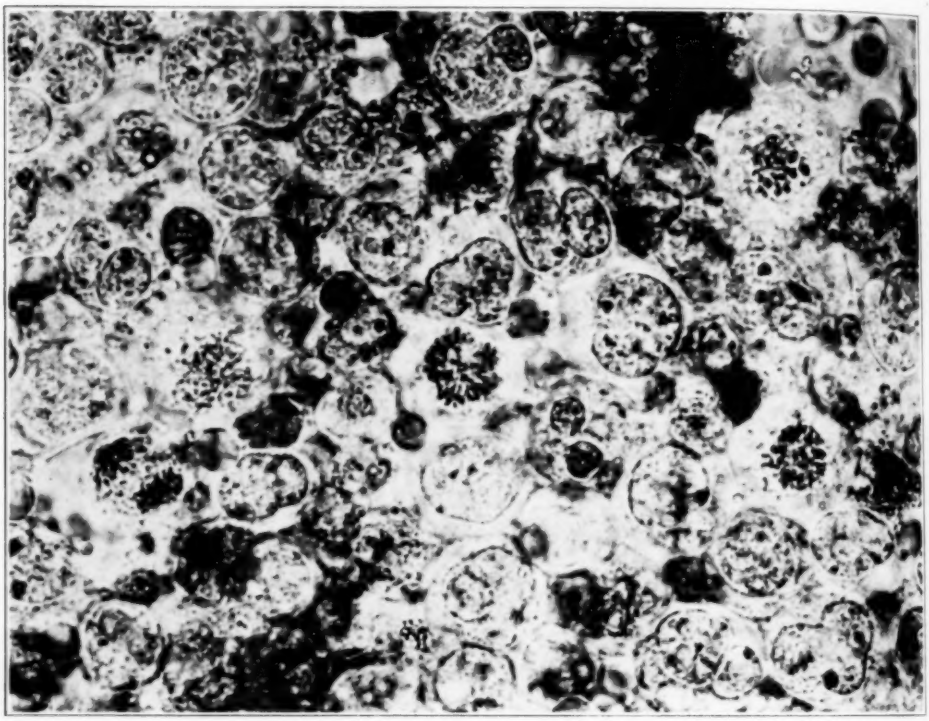

Fig. 12 (case 10).—Supravital preparation of a glioblastoma multiforme showing a field of round and multinucleated cells. Five mitoses are included, four in prophase and one in anaphase; × 850.

under a low power is therefore always wise to make. Such a field as shown in figure 11 *A*, in which numerous phagocytic cells in a necrotic area are easily identified by the neutral red they have taken up, may make one suspicious of a glioblastoma multiforme, but a viable area must be searched for, as illustrated in figure 11 *B*, and here under high oil immersion magnification healthy tissue which allows of a definite diagnosis may be studied.

In figure 12 is shown a photomicrograph of the supravital preparation in the case reported. This area is composed largely of round cells without processes, among which five mitoses happen to be in focus.

SUMMARY

In further illustration of the supravital method for the differential diagnosis of intracranial tumors, ten examples are given, together with the clinical records of the patients. Attention may again be drawn not only to the fact that an immediate diagnosis of the predominating cytology of the lesion may be provided during the course of the operation, but also to the extraordinary difference between the appearance of the cells thus studied and those which pathologists are accustomed to see after tumor fixation.

CENTRAL NERVOUS SYSTEM IN ACUTE PHOSPHORUS POISONING

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REVIEW OF THE LITERATURE

Experimental Investigations.—Phosphorus was one of the poisons used by Nissl [1] in his classic studies of changes in the nerve cells of animals with experimental intoxications. Previous experiments had yielded no valid results because they were based on methods inadequate for the demonstration of nerve cell structures. Nissl found severe changes in nerve cells in rabbits that had been exposed to "subacute maximal intoxication" with phosphorus. There was severe dissolution of the tigroid material and pronounced shrinking of the whole cell. The photomicrographs that Nissl made of these cell changes after phosphorus poisoning have repeatedly been reproduced in later publications as good examples of "toxic changes" in the nerve cells.

These experiments, important as they are from a historical point of view, have almost no significance for present day histopathology, since they are based only on a consideration of individual cells. Nissl himself drew attention later to the fact that the pathology of the nerve cell alone is insufficient, and that all the component parts of the tissue of the central nervous system have to be investigated in any attempt to describe a pathologic process. It was also not taken into account at that time that there may be topographic regions of the brain that are particularly susceptible and may show significant findings when other parts of the central nervous system remain relatively intact. Nissl's experiments on the changes of nerve cells after phosphorus poisoning were repeated by Sarbo,[2] Mourek and Hess,[3] Rosso [4] and many others; but these investigations did not go beyond Nissl's observations.

From the German Research Institute for Psychiatry.

1. Nissl, F.: Die Hypothese der spezifischen Nervenzellenfunktion, Allg. Ztschr. f. Psychiat. **54**:1, 1898; Rindenbefunde bei Vergiftungen, Arch. f. Psychiat. **31**:853, 1898.

2. Sarbo, quoted by Nissl (footnote 1, first reference).

3. Mourek, J., and Hess, P.: Lésions fines des cellules motrices de la moelle épinière dans les divers états d'empoisonnement, Rev. neurol. **5**:667, 1897.

4. Rosso: Alterazioni minime degli elimenti nervosi nell'avvelenamento per fosforo, Riv. di pat. nerv. **2**:535, 1897.

Experimental investigations of the general effects of phosphorus poisoning in animals have been frequently carried out, especially since the important work on fat metabolism by Rosenfeld.[5] He showed, through experimental investigation of the effect of phosphorus poisoning on the starving dog, that the fatty degeneration of the liver is due not to transformation of cell proteins into fat, as Virchow had thought, but to infiltrated fat brought by the blood from the fat deposits of the body to the disintegrating organ. Previous to Rosenfeld's work, Lebedeff [6] had made the important observation that an emaciated patient with phosphorus poisoning did not develop the typical fatty liver. More recently, however, it has been assumed that, besides fat infiltration, phanerosis of fat due to intracellular splitting of high molecular protein bodies (Petri) plays a part in this appearance of fat in the liver in toxic conditions.[7] It was the close relationship of phosphorus poisoning to acute yellow atrophy of the liver that stimulated interest in the effect of this poison. Pathologic changes occur in phosphorus poisoning in various parts of the body, though the liver has received most attention. In the literature on the subject little material is available concerning the effect of large quantities on the central nervous system. The problem of whether and to what extent the central nervous system participates in the lipoid infiltration found in other organs of the body has not been cleared up by adequate histopathologic studies.

The results of histologic studies of the reaction of the central nervous system in experimental phosphorus poisoning are not uniform. Lewy [8] found in rabbits a first stage with proliferation of the small blood vessels, especially in the striatum, and a second stage with diffuse encephalitic changes. He regarded these central changes as secondary to the effect of the poison on the liver. These observations were not confirmed by Kirschbaum,[9] who studied phosphorus poisoning in dogs in the course of an investigation of the influence of damage to the liver

5. Rosenfeld, quoted by Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925.

6. Lebedeff: Woraus bildet sich das Fett in Fällen der akuten Fettbildung? Arch. f. d. ges. Physiol. **31**:11, 1883.

7. Petri, E.: Zur pathologisch-anatomischen Diagnose der Phosphorvergiftung, Frankfurt. Ztschr. f. Path. **25**:195, 1921; Das Verhalten der Fett- und Lipoidsubstanzen in der Leber bei Vergiftungen, Virchows Arch. f. path. Anat. **251**:588, 1924; Pathologische Anatomie und Histologie der Vergiftungen, Berlin, Julius Springer, 1930. Dwyer, H. L., and Helwig, F. C.: Phosphorus Poisoning in a Child from the Ingestion of Fireworks, J. A. M. A. **84**:1254 (April 25) 1925.

8. Lewy, F. H.: Experimentelle und pathologische Untersuchungen über hyper- und hypokinetische Störungen, Zentralbl. f. d. ges. Neurol. u. Psychiat. **29**: 315, 1922.

9. Kirschbaum: Ueber den Einfluss schwerer Leberschädigungen auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:487, 1924.

on the central nervous system. Kirschbaum found a severe degenerative process in the nerve parenchyma without any pronounced fatty degeneration of ganglion cells such as had been found in acute yellow atrophy of the liver. There was also a diffuse dropping out of nerve cells in the cortex and other parts of the gray matter. No predominant or exclusive localization of the pathologic changes could be made out. The cortex was most affected, next the striatum, and then the pallidum and other subcortical gray parts. The foci where nerve cells had disappeared seemed to have a relationship to the blood vessels. There was little reaction on the part of the glia, which was to some extent regressively changed. The vessels themselves showed accumulation of fat in the vessel walls and swelling of the endothelium. The elastica was split up in some cerebral arteries. In one dog, areas of softening as a consequence of hemorrhage from degenerated vessels were observed in the cortex. Accumulation of lipoid material in ganglion cells and glia cells was found only in two dogs and to a very slight degree.

Von Braunmühl [10] has undertaken experimental studies of phosphorus poisoning in rabbits. He proceeded according to the principle of subacute maximal poisoning that Nissl had applied in his experimental studies on the effect of poisons. Von Braunmühl has reported only on his observations in the inferior olives. In a number of cases he found there an early pronounced alteration of the ganglion cells. He drew attention to the fact that the inferior olive cells contain much pigment normally, and that pathologically they react easily with so-called pigment atrophy. This is a pathologic change of the nerve cell which has as one of its component factors an increase of lipoid pigment. It is distinguished from the physiologic increase of lipoid pigment that occurs mainly with advancing age by the fact that the nerve cell shows other changes, such as striking vacuolar degeneration or alterations of the nucleus.

Histopathologic Investigations in Clinical Cases.—Histologic examinations of the central nervous system in persons with phosphorus poisoning have been reported very rarely. This is surprising in view of the fact that symptoms referable to the central nervous system appear frequently and relatively early in such cases. Crouzon [11] mentioned somnolence, paresthesias, delirious states, acute excitement and coma.

Hemorrhages and softenings, especially in the subcortical gray matter, were mentioned in older pathologic reports. Rotky [12] described such a case. A youth, aged 18, committed suicide by swallowing the

10. von Braunmühl, A.: Ueber Ganglienzellveränderungen und gliöse Reaktionen in der Olive, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:621, 1930.

11. Crouzon, O.: Les maladies nerveuses professionelles, Nederl. tijdschr. v. geneesk. **69**:58, 1925.

12. Rotky, H.: Ein Fall von akuter Phosphorvergiftung mit Hirnhaemorrhagie, Prag. med. Wchnschr. **31**:219, 1906.

match heads from two boxes of matches. On the third day a right-sided paralysis developed. The pupils were narrow and reacted sluggishly to light. There were deviation of the eyes to the right, paralysis of the right facial nerve and convulsions of the right arm. The body was in an opisthotonic position, and the head was turned to the right. At autopsy a hemorrhage, the size of a pea, was found near the knee of the left internal capsule, reaching into the globus pallidus. Spielmeyer [13] mentioned the occurrence of purpura of the brain in phosphorus poisoning; he assumed that changes in the coagulability of the blood play a part.

Hammer [14] reported the case of a woman, aged 46, who committed suicide by consuming the match heads from thirty-eight boxes of matches. She died nine hours later. By histologic investigation of the brain with the Marchi method a pronounced fatty degeneration of the cortex was found. The ganglion cells were densely filled with small droplets of fat stained intensely black. Hammer believed that he could rule out the possibility that this fat was within physiologic limits because of the intense stain that it took, and from comparisons with other cases in persons of the same age or older, in which the same histologic method was used. He also found fatty material in the white matter near the cortex, diffusely distributed in various parts of the brain. He referred this fatty degeneration directly to the influence of the phosphorus, and suggested that the early death in this case might conceivably be referred to the changes in the central nervous system.

Elkins and Middlemass [15] examined the brain of a patient who committed suicide during a psychosis of the type of involutional melancholia. This patient swallowed the heads of one hundred and sixty matches. At autopsy, two hemorrhages of the dura mater were found. The right upper temporal gyrus was atrophic. Microscopic investigation showed accumulation of fatty material in the vessels of the cortex and in the ganglion cells, which had well preserved nuclei.

Weimann [16] referred briefly to a case of phosphorus poisoning, in which the patient died about ten days after the intoxication. Both inferior olives were severely affected. The other gray nuclei near the inferior olives were found unchanged.

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13. Spielmeyer, W.: Die Diagnose Entzündung bei Erkrankungen des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **25**:543, 1914.

14. Hammer, H.: Ein Fall von Phosphorvergiftung mit selten rasch letalen Ausgange, Prag. med. Wchnschr. **14**:79, 1889.

15. Elkins and Middlemass, quoted by Rotky (footnote 12).

16. Weimann, W.: Gehirnbefunde bei septischer Allgemeininfektion, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:242, 1928; Intoxicationen in Bumke, O.: Handbuch der Geisteskrankheiten, vol. 11, edited by W. Spielmeyer, Berlin, Julius Springer, 1930.

Summary of Experimental and Pathologic Investigations Reported in the Literature.—The results of the few histologic observations in phosphorus poisoning in men and animals are inconclusive. The experimental observations are contradictory—a fact partly explicable, as Weimann pointed out, by the possibly varying effects of the same poison in different parts of the brain in different species of experimental animals. There is an interesting agreement in human beings and dogs with regard to the involvement of the inferior olive. This observation in phosphorus poisoning would confirm the assumption of the general vulnerability of the inferior olives to which von Braunmühl has drawn attention, and which I have been able to confirm in purulent meningitis.[17]

The problem of whether, in cases of phosphorus poisoning, a fatty degeneration occurs in the brain analogous to that of the liver and other organs has not been settled by the histopathologic investigations. Kirschbaum denied the occurrence of such fatty degeneration in his dogs. Even in osmium preparations he could not demonstrate any considerable accumulation of lipoid material. The human cases mentioned prove very little concerning the problem of the existence of this fatty degeneration in the central nervous system in phosphorus poisoning. They are few and have not been adequately studied with analytic histologic methods. Moreover, the patients were examined at a period of life when the physiologic accumulation of lipoid material in the ganglion cells is so great as to be a source of serious error. In cases of severe psychosis the possible accompanying disorders of nourishment and metabolism have to be considered also. Thus it would be possible in all the human cases so far reported that the accumulation of lipoid material could be accounted for by factors other than the influence of the intoxication. As late as 1904, Obersteiner pointed out that it is frequently overlooked that so much lipoid material can be contained in certain ganglion cells in the involution period.

The time that elapses between the intoxication with phosphorus and death does not seem decisive for the evaluation of the pathologic significance of accumulation of lipoid material in the central nervous system. In the liver, fatty degeneration may be found as early as six hours after the intoxication, according to Winiwarter.[18] In the same way, accumulation of lipoid material in the central nervous system in ganglion cells has been reported by Spielmeyer [19] in morphium poisoning after twelve hours.

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17. Wertham, F.: The Cerebral Lesions in Purulent Meningitis, Arch. Neurol. & Psychiat. **26**:548 (Sept.) 1931.

18. Winiwarter, quoted by Hauser, R.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5.

19. Spielmeyer, W.: Histopathologie des Zentralnervensystems, Berlin, Julius Springer, 1922.

SIGNIFICANCE OF PERSONAL OBSERVATIONS

The following report of a case[20] of phosphorus poisoning is of interest for several reasons. Histologic reports in such cases are very rare and of older date, so that Weimann was justified in making the statement that little is known about changes in the central nervous system in phosphorus poisoning. The more recent cases have been reported only fragmentarily, and no case has been fully described. This patient was relatively young, so that the involutional accumulations of lipoids in the central nervous system did not play a part, as in the cases so far reported. The patient did not suffer from an acute psychosis, but all her life showed a constitutional tendency to depressed moods, during an exacerbation of which she committed suicide. She lived only about six hours after ingestion of the phosphorus.

REPORT OF CASE

An unmarried woman, aged 41, had suffered from frequent depressed moods, during which she would talk very little. The depressed moods lasted about three or four weeks. They were usually precipitated when the patient had had her feelings hurt in some way. As time went on, she became more and more sensitive. She stayed for nine years with one family as a domestic servant. Once in a depressive state she attempted suicide with gas. She ascribed the depressed mood to the fact that she had had to witness the unhappy marriage of her employers. After another suicidal attempt she was admitted to the psychiatric clinic.

During a later admission to the psychiatric division of the Schwabing Hospital, ticlike movements of the shoulders were noticed which ceased when the patient's attention was drawn to them. During her stay in the hospital she made another suicidal attempt by tying a belt around her neck. She said that she felt that she had been neglected in the hospital. The diagnosis was chronic depressive personality.

After a suicidal attempt with poison, the patient was again admitted to the Schwabing Hospital. She was somewhat cyanotic, and lay in bed trembling and huddled together. The heart rate was regular, the pulse strong. Neurologic examination showed no significant features. The patient seemed afraid and answered questions about her state reluctantly. She finally admitted that she had poisoned herself. She had bought rat poison, which she knew contained phosphorus, and had eaten it. The drugstore from which she had bought the poison confirmed her purchase of a phosphorus-containing compound. During the gastric lavage a great deal of brownish mucous material was removed. She was treated with animal charcoal, and given copper sulphate and camphor. After the gastric lavage she did not seem especially sick, had no pains, continued to be very anxious and gave no further information. She did not sleep. The same night she had a sudden collapse. The heart ceased to beat and did not respond to epinephrine.

Autopsy.—There were: fatty infiltration of the liver, heart, kidneys, musculature, etc.; hemorrhages under the pleura costalis and epicardium, and small extravasations in Glisson's capsule.

20. Professor Oberndorfer, of Munich, supplied the material of this case.

Examination of the Central Nervous System.—Macroscopically nothing abnormal was observed on the surface of the brain. The brain was considerably hyperemic. The ventricles seemed to be somewhat distended. When unembedded sections were cut (alcohol-fixed), it was observed that the tissue cut only with great difficulty.

Microscopically, the meninges showed no pathologic changes. In the Nissl-stained preparations made with material fixed in alcohol, many nerve cells in the cortex showed the ischemic type of cell change. This change occurred only locally, chiefly in the upper layers of the cortex (the second and third layers). The Betz cells were intact. Numerous cells also showed the "severe type of cell change" of Nissl. Many cells in the cortex stained very darkly. In numerous places cortical

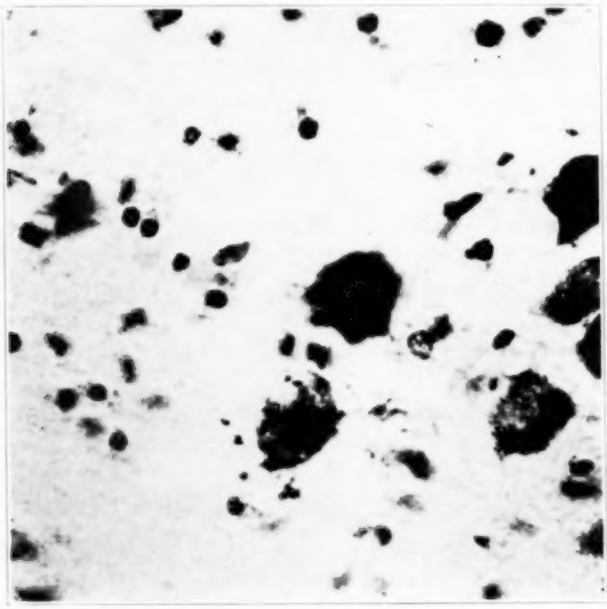

Fig. 1.—Severe cell change with pericellular incrustations in the inferior olive. Nissl stain.

cells showed a typical "water change" (Wasserveränderung), with swelling of the nucleus, which was darkly stained, and of the protoplasm, which showed no Nissl bodies. In some cortical vessels, clusters of bacteria were found in the perivascular spaces (postmortem changes). Nissl preparations sometimes showed in the cortex and in the white matter sharply defined spots that stained only lightly. From their nature and distribution they seemed to be artefacts.

In the basal ganglia, no characteristic changes were found in Nissl preparations. In the globus pallidus, and rather definitely restricted to it, there were very many small round globules, homogeneously stained, of different sizes. In the larger ones a dark nucleus could be seen. The globules stained dark bluish green (Nissl stain). They occurred in large quantities, especially around the vessels. From these characteristics it was possible to identify them as corpora amylacea.

In the cerebellum, many Purkinje cells showed changes similar to the ischemic and homogeneous types of cell changes. Sometimes the nucleus showed various stages of disintegration. In the dentate nucleus many cells were pathologically changed. The nuclei were dark and pyknotic and the cell body light, homogeneously stained and vacuolized.

In the inferior olives a characteristic finding was made. Throughout the whole cross-sections of both olives, cells were found with darkly stained nuclei and with rather coarse impregnations and incrustations in the outer Golgi nets (fig. 1). No sector-like distribution of these cells could be made out; they seemed to be universally distributed through the inferior olives. The incrustations could easily be overlooked when scrutinized only with low power magnification, but were very evident with a higher magnification. Some cells in the substantia reticularis

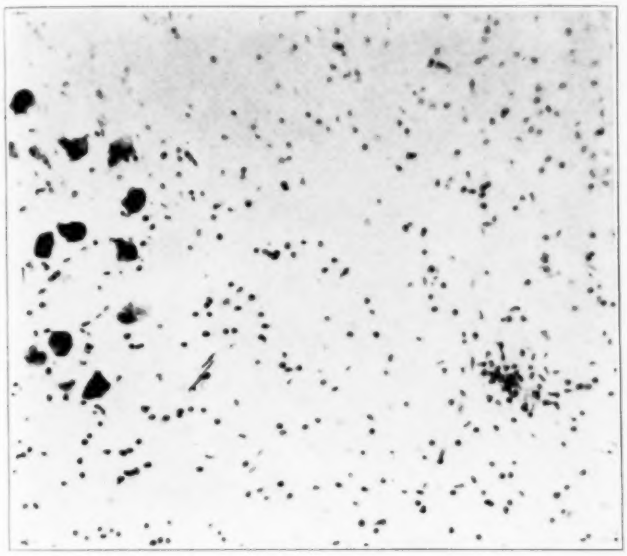

Fig. 2.—Cluster of syncytial glia near the inferior olive. Nissl stain.

also showed a peculiar kind of impregnation, mainly near the circumference of the cell. Small clusters of glia occurred near the olive bands (fig. 2).

In Herxheimer fat preparations, a great deal of lipoid material in fine droplets was seen in the ganglion cells of the cortex. This was especially marked in the frontal lobe (fig. 3). The lipoid material filled the whole cell body, surrounding the nucleus completely. Much fat was also present in the fixed glia cells, some of which had large nuclei. There was a great deal of fat in the vessels also, both in the adventitial spaces and in the endothelial cells. The fat in such vessels seemed collected particularly in regions where branches were given off. There were very few compound granular corpuscles. Comparison of fat preparations in this case with similarly prepared slides made in control cases in persons of the same age showed that the accumulation of lipoid material in the case reported here was very much greater than the amount usually found in persons of that age group.

The cornu ammonis on both sides contained much fat, especially in the end-plate and in the resistant part of the band of ganglion cells. Comparison with fat preparations in other cases showed, however, that the cornu ammonis normally has a great deal of fatty pigment and that this distribution, namely, decidedly more fat in the cells of the end-plate and the resistant band than in the Sommer sector, is a constant characteristic of the cornu ammonis. Less fat was found in the basal ganglia than in the cortex. The claustrum contained much more fat than the putamen and pallidum. In the subcortical white matter much less lipoid material was found than in the cortex, but here also it occurred to a considerable degree in glia cells, vessel walls and perivascular spaces.

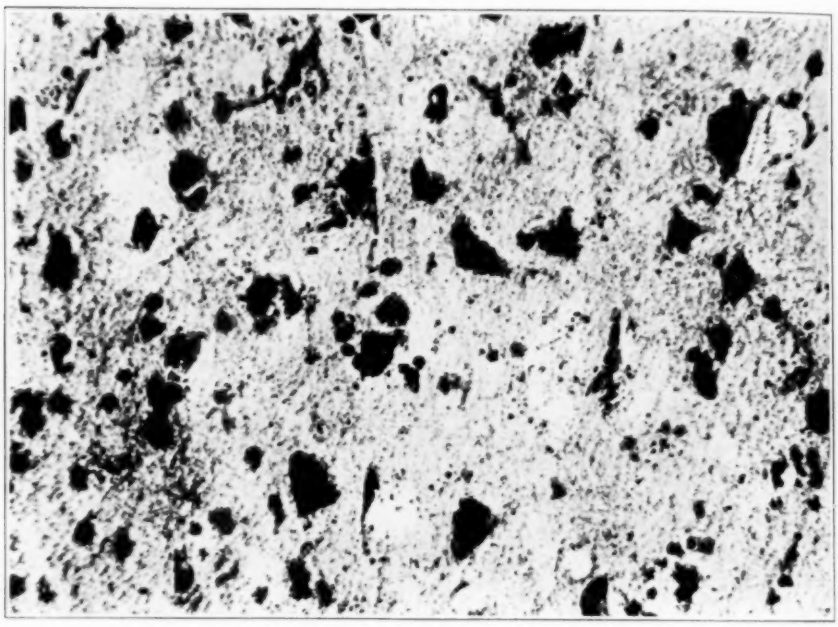

Fig. 3.—Enormous accumulation of lipoid material in nerve cells and glia cells of the frontal cortex. Herxheimer fat stain; the fat appears black in the photograph.

In the calcarine cortex there was little fat in the ganglion cells, although some occurred in the endothelial cells of the vessels. There was much lipoid material in the cells of the dentate nucleus. The Purkinje cells were entirely free. The large Golgi cells of the granular layer, however, lying near the Purkinje cells, and the vessels in that region showed a marked fatty accumulation. This pronounced difference between the Purkinje cells and the Golgi cells (fig. 4) of the granular layer shows the extraordinary independence of the metabolism of the individual cell, for a difference in blood supply cannot play a large part in cells that lie so close together. Summarizing the distribution of the pathologic fat infiltration, it can be stated that those cells that normally contain much lipofuscin—the lipophilic cells of Obersteiner—are the ones mainly affected by the pathologic fat infiltration. The lipophobic cells, on the other hand, are practically spared from any accumulation of fatty material.

There was practically no reaction on the part of the mesenchyma. In the perivascular spaces of the smaller vessels a few infiltration cells, mainly lymphocytes, could be seen.

Comment.—In the evaluation of the microscopic observations in such a case one must be exceedingly cautious. The cell changes in the cortex should be given little stress in view of the fact that water change was also observed in the cortex. The large number of corpora amylacea in the globus pallidus had, of course, no necessary relationship to the pathologic process; but the fact that these corpuscles were so markedly limited to the globus pallidus is interesting because this is not their usual localization (Kawata [21]). Their presence in the globus pallidus is not surprising, however, in view of the fact that other metabolic products, such as iron, pseudochalk, etc., are found there frequently.

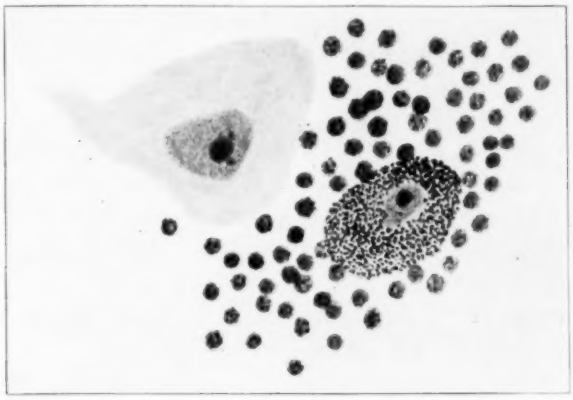

Fig. 4.—Pathologically changed Purkinje cell free from fat and large Golgi cell of granular layer of cerebellum with pathologic fat infiltration, showing contrast between lipophobic and lipophilic cells. Drawn from Herxheimer fat stain; the fat droplets are black.

There are only two features that I consider significant: 1. The changes in the inferior olive. The incrustations of the outer Golgi nets of the ganglion cells of the olive band point to a severe damage of the cells. The fact that the olives are diffusely affected in both longitudinal and cross-sections makes it likely that in this damage to the nervous parenchyma the circulatory factor plays no essential part. In pathologic changes of the olives due to circulatory disorders, usually only parts of the olive band are affected. The occurrence of clusters of glia cells near the inferior olives would also indicate damage to this region. 2. The accumulation of fat in the ganglion cells, the glia cells and the ves-

21. Kawata, N.: Was bedeutet die eigenartige Lokalization der Corpora amylacea? Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:17, 1929.

sels. Comparison with control cases of persons of the same age or older showed that in this condition there is a pathologic amount of fat, such as is not found in the nerve parenchyma normally at this age. The histopathologic demonstration of large fat deposits in the nerve cells, of course, gives no indications concerning the origin of this lipoid material. It seems a permissible assumption that this accumulation of fat in the constituent parts of the brain may well be on the same order as that found in other organs of the body in phosphorus poisoning. It must be remembered, however, that in other intoxications also fatty degeneration of the ganglion cells is found, although it is not usually so pronounced.

CONCLUSIONS

The method of suicide of this patient showed with the precision of an experiment what the effects of phosphorus are on the central nervous system. From this case the following conclusions can be drawn for the general histopathology of the central nervous system: The severe involvement of the nerve cells in the inferior olive in this case shows that this group of cells is apt to be damaged in phosphorus poisoning, as has been shown to be true for exogenic, especially toxic and infectious, conditions.

It may be further regarded as proved by this case that the central nervous system may take part in the pathologic fat infiltration found in other organs of the body in this condition.

The distribution of this fatty infiltrate in the various constituent parts of the nerve parenchyma is of special interest. Those cells that normally contain much lipofuscin, and which Obersteiner therefore called lipophilic, are those most affected by the pathologic fat infiltration. On the other hand, those nerve cells that are usually free from pigment (lipophobic cells) do not participate in this pathologic fat infiltration (area striata, Purkinje cells). The contrast between the lipophobic Purkinje cells and the adjacent large Golgi cells of the granular layer of the cerebellum is especially striking.

Knowledge of such differences in lipoid pigment content, which were first pointed out by Obersteiner, has so far been used only to decide whether or not the appearance of lipoid material in nerve cells or glia cells is within normal limits. It would seem from the present study, however, that these differences in lipoid pigment content and their topographic distribution in the central nervous system, which one may speak of as lipo-architectonics, have also a histopathologic significance.

ACTION CURRENT STUDIES OF SIMULTANEOUSLY ACTIVE DISPARATE FIELDS OF THE CENTRAL NERVOUS SYSTEM OF THE RAT

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Action current studies of the nervous system (exclusively) have employed but one circuit leading away from the responding tissue. Our work with such technic led to findings suggestive of mass responsiveness in the central nervous system and introduced the need for an apparatus that would record simultaneously from more than the one field. We found the solution of this problem in the following apparatus.

APPARATUS AND METHOD

Our recording apparatus consisted of a Westinghouse four element oscillograph, a General Radio type 377 low frequency oscillator and two resistance-coupled amplifiers.

The two oscillograph elements employed with the amplifiers were adjusted to the identical sensitivity of 0.045 inch deflection per milliampere. The element employed with the oscillator gave a sensitivity of 0.01 inch deflection per milliampere. A fourth element which gave a sensitivity of 1.02 inch deflection per milliampere was employed as a check on any possible effects of extraneous influences. All elements were approximately critically damped. Because the impedance of these vibrators was approximately 1 ohm, in order to obtain sufficient current for their adequate operation it was necessary to adopt impedance matching transformers. The latter were made by winding 80 turns of number 18 DCC wire on the coil of American type 854 choke coils. The photographic unit used with the oscillograph was constructed in our laboratory. It carries 400 feet of standard size (35 mm.) motion picture film.

The oscillator, capable of furnishing any frequency between 90 and 80,000 complete cycles per second, was adjusted to provide a frequency of 1,000 complete cycles per second for our 0.001 second interval values.

A wiring diagram of the amplifiers is outlined in figure 1. With an exception relative to the input transformers, both are identical. Since with our technic the input wires of both amplifiers led from the same animal, we could not ground the midtaps of the primaries of both input transformers. Instead we placed in one amplifier an input transformer with a groundable copper shield between the primary and secondary windings rather than with a center-tapped primary. Both amplifiers

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From the Psychopathic Hospital, Iowa City, and the Psychopathic Hospital, Ann Arbor, Mich.

were acoustically and electrically shielded. For each amplifier it was determined that the over-all (amplifier-oscillograph element) upward deflection was 1 mm. for every 5.33 microvolts peak input, so that the potential of the action currents might be measured directly from the film. A frequency-deflection curve for both complete recording units (amplifiers and oscillograph elements) is found in figure 2. There it is seen that the degree of deflection is practically constant for all frequencies between 90 and 900 cycles per second. Our action current frequencies ranged from 430 to 850 per second.

A demonstration of the identity in reproduction of the common input voltages by our two amplifying-recording units is furnished in figure 3. With the amplifiers connected in parallel, the action currents were led off from the tongue by a single pair of electrodes. The resulting identical recordings of the common input voltages by the two amplifying-recording units are striking.

A demonstration of the noninterference in reproduction of different input voltages from closely related sources by our two amplifying-recording units is given in figure 4. The action currents in this figure were recorded with the two

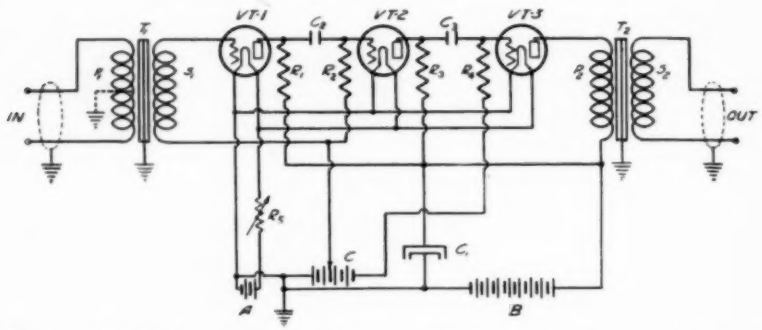

Fig. 1.—Electrical connections of the amplifiers. C_1 designates 4 mfd. by-pass condenser; C_2 and C_3, 0.01 mfd. mica grid-plate coupling condenser; R_1 and R_3, 250,000 ohm noiseless resistor; R_2 and R_4, 2 megohm noiseless resistor; R_5, 2 ohm rheostat; VT_1 and VT_2, G.E.Co. PT 240 high-mu triode, and VT_3, UX 112-A. Power tube. In one amplifier, T_1, there was a Western Electric 226-A input transformer. P_1 stands for 200 ohms impedance; S_1, 50,000 ohms impedance. The primary had a center-tap grounded. In the other amplifier there was a Western Electric 208-P transformer. P_1 stands for 200 ohms impedance; S_1, 100,000 ohms impedance. The shield between the primary and the secondary was grounded. T_2 designates special impedance matching transformer as described in the text; P_2, 10,000 ohms impedance at 100 cycles; S_2, from 2 to 3 ohms impedance at all frequencies used; A, 6 volt storage battery; B, 180 volt "B" battery, and C, 12.5 volt "C" battery, tapped at 1.5 volts.

sets of electrodes placed on the same contracting forearm. The dissimilarity of the resulting action current patterns is apparent.

All leads running to and from the instruments were protected by grounded copper sheathing. The oscillator and the amplifiers were operated from batteries. The "A" battery for each amplifier was grounded. Both sets of electrodes consisted of platinum wires, sharpened to needle points, 3 mm. long and 3 mm. apart.

The animals used were thirty full grown white and hooded rats. The fields were prepared for the insertion of the electrodes, and certain ablations, which will

be described later, were made with the animal under general ether anesthesia. Experiments were not attempted until the observable effects of the latter had worn off. The rat's head was immobilized in such a way as to permit free action of the trunk and extremities. Following the topography of Fortuyn,[1] all of the cortical fields (areas) were explored. Records were obtained from both ipsolateral and contralateral homologous and heterologous fields.

In keeping with our earlier study [2] on the action current source, we have again concerned ourselves with the organismal activities of the animal.

EXPERIMENTAL DATA

It may be repeated that during voluntary movements of the rat we were able to record the subsequent action currents from two varyingly

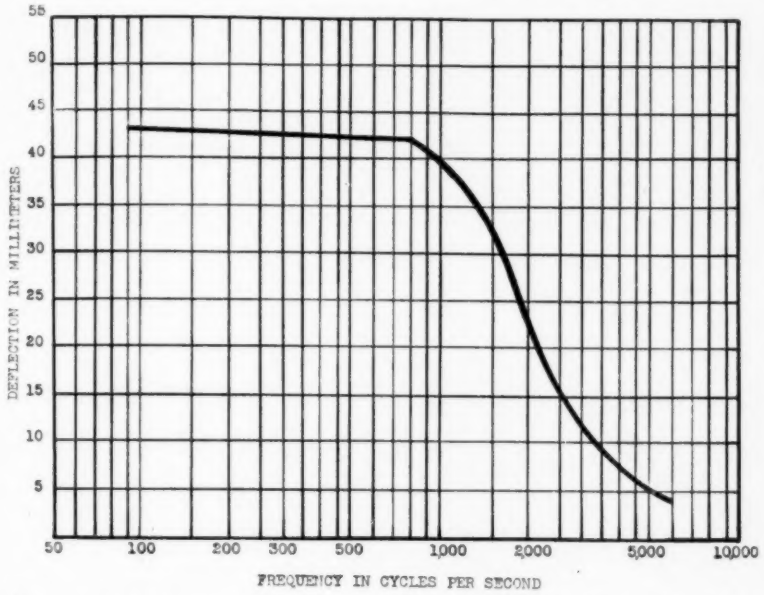

Fig. 2.—The frequency-deflection curve for a constant input voltage of the amplifying-recording units.

separated central nervous system fields. Comparative studies of these action currents have been made from the standpoints of synchronization, frequency, intensity, duration, phase relationships, general patterning and instant of appearance.

For contralateral homologous fields, synchronization and isomorphism were striking in the motor fields (fig. 5). Similar kindred relationships, which were less marked, were noted in the visual and

1. Droogillver Fortuyn, H. B.: Cortical Cell-Lamination of the Hemispheres of Some Rodents, Arch. Neurol. & Psychiat., Path. Lab., London **6**:221, 1914.

2. Travis, L. E., and Dorsey, J. M.: Mass Responsiveness in the Central Nervous System, Arch. Neurol. & Psychiat. **26**:141 (July) 1931.

common sensory fields (fig. 6). These relationships were most wanting in the compared auditory fields. As a rule, in these records we were unable to determine the exact instants for the inception of the action currents because they presented an indeterminate gradual rather than an abrupt moment of appearance (fig. 7). Both with the corpus callosum completely severed and separated and with its posterior five-sixths severed and separated, with one notable exception, the same results obtained when the action currents of similar fields were compared. Here a striking suddenness for the inceptions of the recorded action currents was the rule (fig. 8).

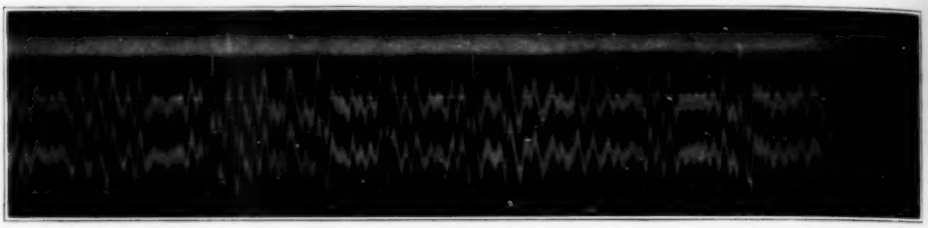

Fig. 3.—A sample of recordings of common input voltages (action currents led off from the tongue by a single pair of electrodes) by the two amplifying-recording units when the amplifiers were connected in parallel.

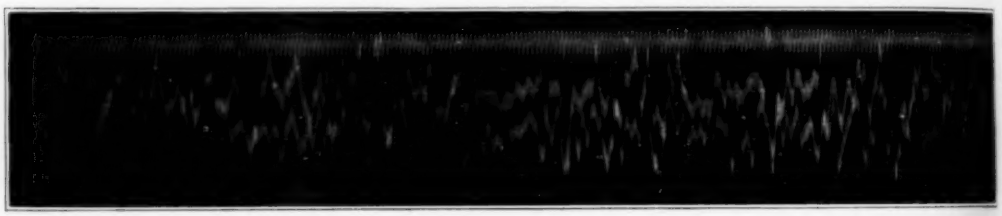

Fig. 4.—A sample of recordings of different input voltages from closely related sources (action currents recorded with the two sets of electrodes on the same contracting forearm).

In both the ipsolateral and the contralateral heterologous fields a distinct departure from these tendencies was noted in that asynchronization and anisomorphism were the rule (fig. 9). The latter were noted further in the similarly compared action currents from the fields of the brain and cord (middorsal level), of the right and left cord (middorsal level), and of the brain and peripheral nerve (sciatic). Compared action current records from the contralateral visual fields and from the contralateral common sensory fields with the anterior one third (frontal pole) of the right hemisphere and with the anterior one third (frontal pole) of the left hemisphere, respectively, ablated likewise

showed these asynchronous and anisomorphic relationships. Further, with the right hemisphere ablated, the compared left motor and visual fields action currents were asynchronous and anisomorphic; with four fifths of the right hemisphere ablated the compared left common sensory and visual fields action currents were asynchronous and anisomorphic. Action currents obtained from fields in the neighborhood of lesions were commonly more abrupt in appearing, of greater amplitude and of earlier appearance than were those with which they were compared.

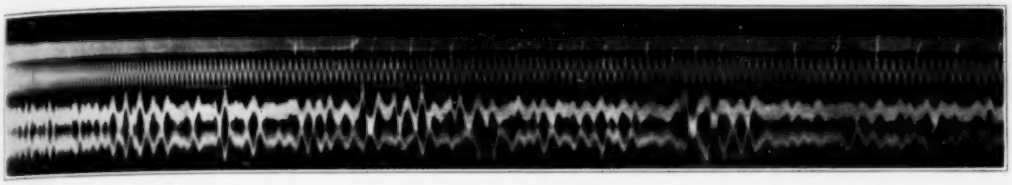

Fig. 5.—Record of the action current patterns from contralateral homologous (motor) fields showing high degrees of synchronization and isomorphism. (In order to make the identity of the two action current patternings the more obvious, the polarity of the input wires of one amplifier was reversed with respect to that of the input wires of the other amplifier, so that the action current potentials appear to be 180 degrees out of phase. In this, as in the following records, reading from above downward, the first line is the check line, the second is the time line, the third is an action current pattern from the left cerebral hemisphere, and the fourth is an action current pattern from the right cerebral hemisphere.

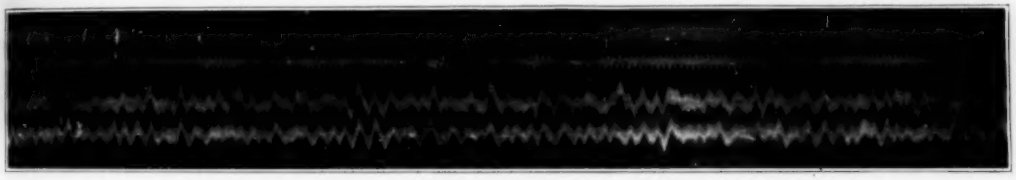

Fig. 6.—Record of action current patterns from contralateral homologous (visual) fields showing lesser degrees of synchronization and isomorphism.

Uninterpreted, but of arresting interest, were periodic single diphasic waves occurring infrequently in the brain, cord and nerve at a rate of from 70 to 100 per second.

No consistent differences were found either between the action current frequencies of the left and those of the right cerebral hemispheres or between the action current frequencies of one field and those of another in the same hemisphere.

COMMENT

We have observed that the degree of similarity in the action current pattern varies in direct proportion to the propinquity of the compared

contralateral homologous fields—thus, the directly opposed motor fields afford the greatest similarity, and the auditory, or the most disparate of the compared contralateral homologous fields, offer the least similarity. That these relationships are not incidental results of structural propinquity, but rather that they would appear to have a physiologic basis, is indicated by the fact that when the two sets of

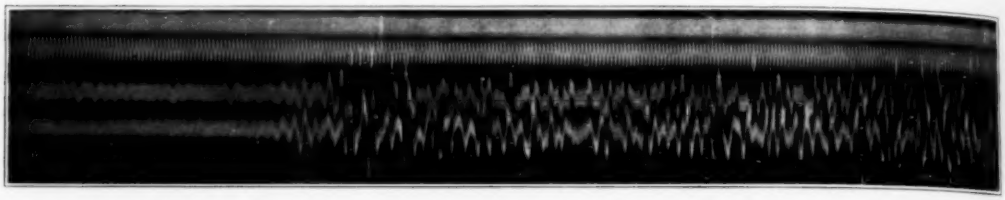

Fig. 7.—Record of action currents from contralateral homologous (auditory) fields showing the great difficulty connected with determining the exact instants of appearance of the action currents.

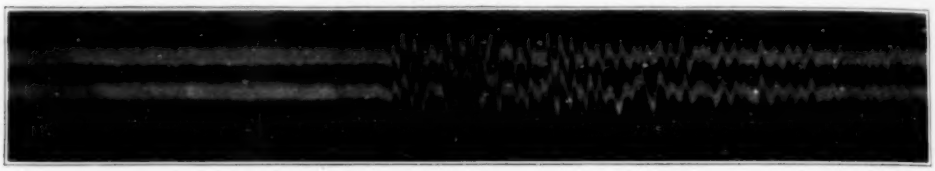

Fig. 8.—Record of action current patterns from contralateral homologous (motor) fields following complete severance of the corpus callosum. It shows the abrupt inception of the action currents as well as the unaffected similarity of the two action current patterns.

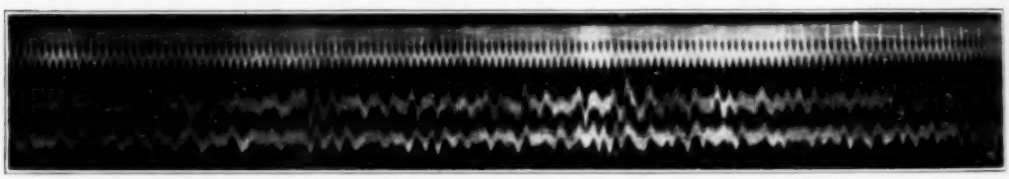

Fig. 9.—Record of action current patterns from contralateral heterologous (left visual and right motor) fields showing the greatest want of synchronization and isomorphism.

electrodes were placed shoulder to shoulder in ipsolateral heterologous fields, dissimilar action current patterns were recorded. Of interest here are certain structurally related observations.[3] The function is

3. Malone, E. F.: Functional Significance of Histologic Character in Preganglionic Visceral Neurons, Arch. Neurol. & Psychiat. **22**:295 (Aug.) 1929.

related to the size, form and internal structure of the neuron. The size of the cell body with its processes is interpreted as an indication of the extent of the neuron's activity. Believed to be resident in the Betz cells with their large bodies and long processes is an unusual capacity for resisting fatigue and maintaining a uniform high irritability. Moreover, neurons of large cell bodies are found to be characteristic of centers employed in stable reactions and tend to direct the nerve impulses into relatively fixed paths. It is conceivable that as the final common motor path is approached, the right and left motor frequencies in some way, possibly by the former accepting the latter's rhythm, coalesce to result in the perfect synarchy which is essential for unified control. It is thought-provoking to view this process as a dynamic act of unification on the parts of the two hemispheres producing a oneness in their outputs. Such a theory may be significant for the problem of hemispheric dominance.

Complete severance, except for the anterior one-sixth, and complete severance of the corpus callosum did not affect the similarity of the action current patterns of the two motor fields. This may indicate that the corpus callosum alone is not responsible for the binding together of the two motor fields to insure their unified functioning. Such a conclusion has recently been supported by the findings of Dandy,[4] who reported that for the human being the entire body of the corpus callosum has been split in the midline without any disturbance of function that could be detected.

The significance of the recorded effects of the removal of nerve tissue on the action current patterns is not clear.

Of possible significance for the understanding of the mechanism of cerebral dominance is the consistently recorded absence of any characteristic pattern of action currents. This applies also to the frequency, amplitude, duration and inception of appearance of the action currents from either hemisphere.

SUMMARY

1. An apparatus has been described for recording simultaneously action currents from two varyingly separated central nervous system fields.

2. We have recorded both synchronous and isomorphic and asychronous and anisomorphic action current patterns from compared fields of the central nervous system.

4. Dandy, W. E.: Changes in Our Conceptions of Localization of Certain Functions of the Brain, Am. J. Physiol. **93**:643 (June) 1930.

3. No interpretable differences were found either between the action current characteristics of the left and those of the right cerebral hemisphere, or between the action current characteristics of one and of another field in the same hemisphere.

4. Complete anteroposterior severance of the corpus callosum did not affect the similarity of the action current patterns of the two motor fields; it did introduce a striking abruptness of inception of the action currents.

5. Fresh experimental lesions tended to affect the action currents in three ways: (1) by producing an abruptness of their inception, (2) by hastening their appearance and (3) by increasing their amplitude.

6. Periodically but infrequently occurring single diphasic waves of a rate ranging from 70 to 100 per second, not related to any controlled or detected activity of the animal, were recorded from the brain, spinal cord and peripheral nerve.

7. From the data were suggested certain leads of possible significance for the problem of neurophysiologic dominance.

CRANIAL HYPEROSTOSIS

ASSOCIATED WITH AN OVERLYING FIBROBLASTOMA

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AND

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PHILADELPHIA

Hyperostosis of the skull associated with an underlying fibroblastoma has been reported in a good many instances. It is recognized that in a small number of cases of fibroblastoma of the meninges there is an accompanying cranial thickening, with the presence of tumor cells within the thickened bone. The mechanism involved in the production of hyperostosis is still unsettled, but the clinical fact remains that hyperostosis and a subjacent fibroblastoma are sometimes associated.

That an extensive thickening of the cranium may result from a fibroblastoma lying on the skull has not as yet been recognized. It is for this reason that we record an unusual case in which there was a fibroblastoma lying on the skull, accompanied by a pronounced hyperostosis of the underlying bone. This is the first example of this sort of which we are aware. Trauma seemed to play a rôle in the formation of the tumor in this case.

REVIEW OF THE LITERATURE

The cases of hyperostosis associated with fibroblastoma have been reviewed in several articles, but it seems worth while to record them once more, both for the sake of completeness and for the purpose of clarity. Virchow [1] (1864) described a psammoma of the dura at the base of the brain overlying an exostosis of the sphenoid bone which followed a trauma. It lay behind the crista galli in the midline, and, from the illustration, the bony exostosis apparently reached a considerable size.

The first case reported in detail in the literature is that of Spiller [2] in 1899. The patient was presented by him at the April, 1899, meeting of the Section on General Medicine of the College of Physicians of

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1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864-1865, p. 115.

2. Spiller, W. G.: Tr. Coll. Phys., Philadelphia **21**:191, 1899; Med. Rec. **55**:757 (May 27) 1899.

Philadelphia to show the enlargement of the left side of the head. The case, after the operation, was reported by him in association with Stern and Kirkbride at the May, 1899, meeting of the section. The patient had been under the care of Spiller and had been referred by him to Stern for operation. The pathologic report was given by Kirkbride, pathologist to the hospital. Merely the title of the paper with the names of the authors is given in the *Transactions of the College of Physicians, Philadelphia*.[2] An abstract of the paper,[2] however, published in *The Medical Record*, stated:

> College of Physicians of Philadelphia, Section on General Medicine.—At a stated meeting held May 8th, Drs. W. G. Spiller, M. J. Stern and T. S. Kirkbride reported a case of focal intracranial pressure, and they exhibited the brain from the patient. The case was that of a man who, sixteen years previously, had fallen and injured the left side of his head. After eight years a swelling was noticed in this situation, and several years later paresis in the right lower extremity, and later in the right upper extremity also. Headache and vomiting were superadded, speech became paraphasic, and finally a convulsion occurred. On ophthalmoscopic examination bilateral optic neuritis was found. Operation was decided upon; a segment of greatly thickened and infiltrated bone was removed from the calvarium, and a new growth found in the cortex of the left motor area. Hemorrhage was profuse and death occurred a few hours after the operation, from loss of blood and shock. On histological examination the growth was shown to be an endothelioma. In addition an unsuspected melanotic sarcoma of one choroid was found.

This case was also reported in detail in 1907 by Spiller,[3] in connection with another case.

Brissaud and Léreboullet[4] (1903) reported three similar cases. In the first case, that of a man, aged 20, there was a marked swelling of the left frontoparietal region, stopping abruptly at the midline and at the occipital bone. In the second case, that of a woman, aged 34, there was a conelike elevation in the right frontoparietal region, which was hard and painless and had been present since 3 years of age; at autopsy, the entire dura over the right hemisphere was taken up by small and large tumors, often calcified at the point of their attachment to the dura, the largest tumor being at the base of the brain and at the anterior part of the temporal fossa. The tumors were described as angiolithic sarcomas. The bone was not examined histologically.

Another case of hemicraniosis in the right frontal region was reported by Parhon and Nadjede,[5] who discovered the bony enlargement and an underlying tumor, the size of a small orange, in the right frontal lobe in a patient aged 63. The tumor was a psammoma or an angio-

3. Spiller, W. G.: Hemicraniosis and Cure of Brain Tumor by Operation, J. A. M. A. **49**:2059 (Dec. 21) 1907.

4. Brissaud and Léreboullet: Deux cas d'hémicraniose, Rev. neurol. **11**:537, 1903.

5. Parhon, C., and Nadjede, G.: Sur un nouveau cas d'hémicraniose, Rev. neurol. **13**:1017, 1905.

lithic sarcoma. The bone showed a few excrescences on its inner surface, but was not examined histologically.

The first detailed study of the bony hyperostosis in these cases was made by Barling and Leith,[6] who reported the case of a man, aged 30, who had a tumor overlying the left precentral convolution, accompanied by bony thickening of the overlying skull. The tumor was diagnosed as a sarcoma of the endotheliomatous type arising from the pia mater. The inner table of the thickened cranium was extensively destroyed by tumor growth, which penetrated into some of the inner spaces of the diploe and was found penetrating as far as the outer table. The entire thickness of bone showed invasion by tumor cells. There was increased porosity of the bone, caused by the accumulation of tumor cells lining the bone spaces. No osteoblasts were seen. Leith believed that the microscopic evidence indicated a direct extension of the tumor along the sheaths of the blood vessels, through the dura and into the bone.

Spiller[3] (1907) made another important contribution to the subject by calling attention to the rôle played by trauma in the hyperostosis. He reported two cases. In case 1, the patient had received a blow on the head sixteen years previously; this was followed by an enlargement of the parietal portion of the skull eight years later, with paresthesias of the right side and convulsions. The tissue of the scalp overlying the tumor was much indurated and fibrous. The outer surface of the skull was studded with nodular exostoses, and the inner surface was adherent to the dura. Beneath the thickened bone lay a large, gray, encapsulated tumor, which was adherent to the dura and falx. Apparently the bone in this case was not examined histologically. In Spiller's second case, a hard swelling had been noticed in the left parietal region for six or seven months. There were a right hemiparesis and some aphasia. At an operation, Frazier removed the tumor of the skull under which lay an endothelioma. The bone was examined histologically and was found to be free from tumor cells. Spiller stated at this time:

> In both my cases a history of head trauma was obtained: in the first it occurred about eight years before the enlargement of the head was noticed; in the second, only a short time previously. It is not improbable that these injuries were at least the predisposing cause of the bony proliferation.

Trauma is mentioned as a causative factor in the next case, reported by Fuchs[7] (1910) from the service of von Eiselsberg. The patient had struck his head against a cellar door twenty years previously. Over the tumor, an endothelioma, which lay in the motor area, was a bony hyperostosis that on microscopic examination showed tumor cells in its meshes.

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6. Barling and Leith: Removal of Cerebral Tumour (Endothelioma) Which Had Invaded the Overlying Cranial Bone, Lancet **2**:282, 1906.

7. Fuchs: A Successfully Operated Case of Brain Tumor, Wien. klin. Wchnschr. **23**:1701, 1910.

Tattersall [8] (1917) reported the case of a man, aged 25, who three years before admission to the hospital had been knocked down by a horse and stunned, but did not lose consciousness. Loss of sight developed in a short time, with mental disturbances and weakness of the left arm and leg. At necropsy a bony tumor was found invading the skull from the base half way to the vertex. "There was a somewhat flattened osseous plaque consisting of cancellous growth of bone from both surfaces, not adherent to dura mater." There was a tumor of the left cerebral hemisphere, which was found to be an endothelioma.

An endothelioma associated with a hyperostosis, in which no tumor cells were found, was reported by Ashhurst [9] in 1920. The patient was a man, aged 31, who suffered from attacks of jacksonian epilepsy. A sessile exostosis, about 5 cm. in diameter, was found in the right parietal region. There was no history of injury. Roentgen examination revealed rarefaction of the inner table of the skull. A tumor was removed from the right motor area at operation. It was examined by Dr. Spiller and found to be an endothelioma. The bone was examined by several competent observers, and no tumor cells were found. This case was of importance to Spiller because it established the fact that the bony enlargement above a fibroblastoma may take place without infiltration by tumor cells, indicating that the processes are associated. A similar case, which has not previously been quoted, was reported in the previous year by Sternberg [10] (1919). In this case there was an endothelioma of the parietal lobe, associated with a cone-shaped enostosis of the overlying parietal bone. The bony enlargement, curiously enough, involved only the inner table, which indented the surface of the dura and tumor. Sternberg was unable to find evidence of infiltration of the bone by tumor cells. He believed that the chronic irritation of the enostosis provoked the dura to the formation of a tumor, and that the endothelioma followed the bony enlargement. He mentioned the possibility of trauma as a factor in causing the bony enlargement, but there was no such history in his case.

It is possible that the case reported by Rand [11] (1923) is similar to those reported by Ashhurst and Sternberg, though the bone was not examined carefully enough to speak with assurance. Rand removed a piece of bone from the vertex of his patient three years after the latter had noticed a small bony swelling in that region. The report on the

8. Tattersall: A Case of Cerebral Tumour with Tumour of the Skull, J. Ment. Sc. **63**:250, 1917.

9. Ashhurst, A. P. C.: Case of Jacksonian Epilepsy Caused by Brain Tumour, Ann. Surg. **72**:402, 1920.

10. Sternberg, H.: Ein Endotheliom der Dura über einer inneren Exostose des Schädeldaches, Berl. klin. Wchnschr. **56**:178 (Feb. 24) 1919.

11. Rand, C. W.: Osteoma of the Skull, Arch. Surg. **6**:573 (May) 1923.

bone at that time was a "benign osteoma showing irregular growth of bone." With the persistence of symptoms and the recurrence of the bony enlargement, an operation was again performed about three and a half years later, and a large and extensive osteoma removed. No exploration of the cortex was made at this time. Two years later, a large endothelioma was removed from the left frontal area. Unfortunately, the bone was not examined after the first operation. It is possible that the soft tumor was present at the time of the first operation, but we cannot be certain of this. On the other hand, the possibility exists that the bony tumor preceded the soft tumor in development, and that the latter may have developed after the osteoma.

The next important contribution to the subject was made by Cushing[12] (1922), who reported twenty cases of meningiomas with bony hyperostosis. In every case, tumor cells were found in the thickened bone. Of the twenty cases reported, eight were of the flat type of meningioma (méningiome en plaques) and twelve of the common type. Cushing pointed out that the meningiomas en plaques were more commonly associated with hyperostosis than the other type, and that they are often distinguished only by the accompanying bony thickening. Cushing expressed the belief that the bony hyperostosis is caused by the underlying tumor. "This process is due to invasion of the bony canals by tumor cells, with resultant stimulation of osteoblasts, and the production of the new bone." The mechanism of the production of the hyperostosis is stated in greater detail as follows:

> Under the influence of intracranial tension the tumor cells . . . . become crowded into and through the vascular dural spaces, and finally into the canaliculi of the bone. In consequence of this, the bone becomes irritated, with subsequent osteoblastic proliferation which provokes the hyperostosis. There can be little doubt that the thickening occurs in this way, but intracranial tension can have nothing to do with it, in view of the fact that the flat endotheliomas which do not increase tension, are, as we have seen, those which most often tend to invade the bone.

Cushing, therefore, stated clearly the cause for the production of the hyperostosis by invasion of the bone by tumor cells.[12a]

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12. Cushing, Harvey: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:139 (Aug.) 1922.

12a. It is questionable, in our opinion, whether the tumor cells cause osteoblastic proliferation and deposit of bone as is claimed. We have at hand a recent case in which there was a prominence in the temporal bone of one side, caused not by a hyperostosis, but by a bowing out of the temporal bone. Beneath the bony convexity was an extradural fibroblastoma. Roentgen examination showed not thickening, but thinning. Microscopic studies of the bone showed invasion by tumor cells, and evidence of extensive destruction of bone. Osteoclasts were numerous, but osteoblasts were not seen. Here, then, is an instance of invasion of bone by fibroblastoma with destruction rather than proliferation of bone. It throws some doubt on the provocative action of the tumor cells in producing the hyperostosis.

Penfield [13] (1923) made a careful study of ten tumors with hyperostosis. He came to the conclusion that:

> Whatever may be the etiology of these tumors, the cranial prominence is secondary to invasion of the skull by the intracranial tumor. It is incorrect to assume that the cranial and intracranial tumors are of entirely different nature. They are the same except that the growth of the former is accompanied by bone formation.

Penfield found a record of trauma in only two of his ten cases. He stated that:

> The neoplasm invades the overlying skull. This is associated with absorption of bone and laying down of new bone. In early cases, that is of a year or two standing, the bones tend to be more porous. In long-standing cases, the bone is usually more eburnated. The whole bone pattern becomes altered, the external table is absorbed and remade so that the outer surface of the skull as a rule, slopes gradually up on the neoplastic prominence. Endothelioma cells are everywhere filling all the Haversian canals and spaces. But there lie between these cells and the bone, cells resembling connective tissue. At the apex of the tumor, beneath the scalp, there is invariably a pad of endothelioma. Here the bone proliferation is most active, and here the connective tissue cells just mentioned, are most in evidence surrounding the newly formed bone spicules.

Penfield expressed the belief that the cells covering the newly forming areas of bone are osteogenic cells "which resemble the fibroblasts derived from periosteum and bone tissue during ordinary bone regeneration, and are derived either from the outer layers of the dura or from the bone itself." He expressed the opinion further that, while it is usually impossible to elicit a history of trauma, this factor may in some way be of etiologic importance.

The views of Cushing and Penfield coincide so far as they claim that the cranial hyperostosis is secondary to an invasion of the bone by the underlying tumor. Cushing expressed the belief that the increased intracranial pressure is important in forcing the tumor cells into the bone canaliculi, whereas Penfield did not state just what are the factors that prompt the invasion of the bone by some tumors and not by others. Both seem to agree that the bony thickening is due to the invasion of the cranium by tumor cells. Penfield, however, acknowledged the possibility of trauma as the cause of the bony enlargement in some cases.[14] Phemister [15] (1923) was in agreement with this view. He stated that:

> . . . the primary tumor arises inside the dura from cells connected either with its inner lining or with the arachnoidal villi. . . . As the tumor grows

13. Penfield, W. G.: Cranial and Intracranial Endotheliomata—Hemicraniosis, Surg., Gynec. & Obst. **36**:657, 1923.

14. Penfield, quoted by Spiller, W. G.: Cranial Hyperostosis Associated with Underlying Meningeal Fibroblastoma, Arch. Neurol. & Psychiat. **21**:637 (March) 1929.

15. Phemister, D. B.: The Nature of Cranial Hyperostosis Overlying Endothelioma of the Meninges, Arch. Surg. **6**:554 (March) 1923.

its cells penetrate the dura and invade the overlying bone, throughout which they spread. Instead of eroding the skull, the tumor exerts a stimulating influence upon it. The result is the formation of a hyperostosis, which consists of two intermixed portions, namely endothelial tumor and a newly formed nontumorous framework.

Phemister expressed the opinion that "the new bone is not tumorous in nature, and is merely ossified stroma of the invading endothelioma." That it does not originate from the tumor cells is shown first by the fact that the intracranial portion of the tumor does not ossify, and again by the method of growth of the new bone, growing out of and radiating from the old, and suggesting, therefore, an origin from the skull rather than from the tumor. Growth takes place apparently from both the internal and the external surfaces.

A slightly different view was advanced by Trossat [16] (1924) and concurred in by Martin and Dechaume [17] (1927). Trossat expressed the opinion that the meningeal tumor invades the bone, advancing through the haversian canals and causing a proliferation of bone. The new bone arises from the normal bone cells and not from the tumor cells. There is, moreover, in these bones a congestion and passive hyperemia which increases the proliferative faculties of the bone. The tumor, as it advances, causes a rarefaction of the bone. The osteoblasts are then excited to produce bone. Martin and Dechaume reported a case of meningioma and hyperostosis in the right parietal region. They expressed the belief that the hyperostosis is due to invasion of the bone by tumor cells, but they were inclined to stress the circulatory changes that take place in the bone. They expressed the opinion that a superficial tumor may lead to circulatory disturbances in the vessels that come from the diploe to the dura. There then results a regional blockage of veins and a hemorrhagic stasis, which somehow or other is conducive to the proliferation of bone.

Weiser [18] (1925) reported two cases of endothelioma with overlying hyperostosis and with changes in the bone in the outer portions of the soft tumor.

Taylor [19] (1928) agreed that the formation of new bone is due to a stimulating effect of the tumor cells on the bone cells. He attributed the radial arrangement of the newly formed bone to the fact that the tumor cells spread along the newly formed blood vessels in the tumor.

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16. Trossat, quoted by Martin, J. F., and Dechaume, J.: Parois craniennes et tumeurs méningées, Bull. Assoc. franç. p. l'étude du cancer **16**:598, 1927.

17. Martin and Dechaume (footnote 16).

18. Weiser, Arthur: Zur Kenntnis der Knochenbildung an der zerebralen Fläche der Duraendothelioma, Deutsche Ztschr. f. Chir. **192**:405, 1925.

19. Taylor, Julian: Invasion of the Skull by Dural Tumors, Brit. J. Surg. **16**:4, 1928.

In a more recent paper, Spiller [20] (1929) stated that there is no doubt that tumor cells of the same character as those of the fibroblastoma may be found in the hyperostosis, "but I have not believed that it has been fully established that the enlargement of bone is invariably secondary to the formation of tumor of the dura." Spiller went on to say:

> I am not at all sure that in the reported cases in which the bone has been found to contain tumor cells, the proof has been offered that the tumor formed first and the enlargement of the bone was secondary. This may be possible in many cases, but it seems to me also possible that the enlargement of the bone may come first.

Spiller, therefore, expressed the belief that the bony enlargement may be primary in some cases, and that this enlargement may be secondary to trauma. So far as we know, Spiller did not state that all cases of fibroblastoma with cranial hyperostosis are associated with a history of cranial trauma, but rather that in a small group of cases of this sort, trauma may be an important factor in the bony enlargement, and not infiltration by the tumor cells.

A new view was advanced by Kolodny [21] (1929), though part of his evidence had been previously adduced by Trossat. Kolodny expressed the opinion that:

> . . . the bone proliferation precedes the actual infiltration of the bone by the tumor cells, and probably is the result of an early, especially slowly, progressing dilatation of the blood vessels in the portion of the cranium overlying the meningioma, while the subsequent infiltration of the bone by tumor leads to bone destruction.

According to this view, therefore, the bony hyperostosis does not result from the infiltration by tumor cells, but occurs before the tumor cells enter the bone. Kolodny studied ten bone flaps in cases of meningioma with bony changes, and found the first change to be a dilatation of the venous channels of the skull, seen especially at the periphery of the affected portion of the bone. There then follows a deposit of new bone on the external and internal surfaces of the skull. Then comes the infiltration with tumor cells. These first appear in the diploe, and spread to the external and internal tables along the haversian canals and between the bony lamellae. The tumor cells cause no proliferation of bone, but absorption of bone by pressure. The possibility of local circulatory disturbances in the bone had been mentioned previously by Schlesinger and Schüller [22] (1914), who believed that the endothelioma

20. Spiller (footnote 14).

21. Kolodny, Anatole: Cranial Changes Associated with Meningioma: "Dural Endothelioma," Surg., Gynec. & Obst. **48**:231, 1929.

22. Schlesinger, H., and Schüller, A.: Ueber die Kombination von Schädelhyperostosen und Hirngeschwülsten, Neurol. Centralbl. **33**:82, 1914.

might cause a local hyperemia of the bone and a venous stasis that could eventually become a stimulus to the formation of a bony hyperostosis. In this particular, Kolodny differed radically from Penfield, Cushing and others, who believed that the infiltration of the tumor stimulates the bone cells to form new bone.

Recently, Winkelman [23] (1930) reported a case of fibroblastoma, which lay at the base of the brain and infiltrated the bones at the base of the skull. The tumor occupied the left frontotemporal area, was a typical fibroblastoma, and was associated with a thickening of the bone in the roof of the left orbit. Winkelman found tumor cells in only two minute areas of bone.

REPORT OF CASE

Tumor of the left frontal bone of five years' duration, following trauma to the head. Ipsilateral symptoms: facial paralysis of central type, hemiparalysis and atrophy of the tongue, paresis and atrophy of the upper extremity, bilateral impairment of hearing. Increased intracranial pressure. Left frontal craniectomy. Uneventful recovery. Pathology: fibroblastoma of the scalp; cranial hyperostosis underlying the tumor.

History.—C. A., aged 23, an automobile mechanic, single, was admitted to the neurosurgical department of the University Hospital on Nov. 26, 1930, in the service of Dr. Charles H. Frazier, because of a bony swelling in the left frontal region. At the age of 2, he had fallen against a hot stove, striking the left side of the forehead. No serious results followed the injury aside from a small burn, the scar from which was still present. From early childhood he had suffered from poor vision, especially in the left eye, which was further hampered by an external strabismus. Glasses had been worn from the age of 7. Aside from a rather severe attack of influenza at the time of the epidemic in 1918, he had enjoyed good health.

In 1925, the patient received what he considered to be an insignificant bump on the left side of the forehead. The small swelling resulting from the contusion, however, did not recede within the usual time, but became firm, and slowly and progressively increased in size during the next five years. There was no tenderness or pain associated with the swelling. It was not until July, 1930, that he became so impressed with the size and the progressive growth of the tumor that he consulted his family physician, Dr. I. Morgan, of Nanticoke, Pa. Roentgen examination of the head at this time revealed a bony tumor of the skull.

Secondary complaints, the onset of which had not been closely observed by the patient, were of particular interest. Shortly after the appearance of the cranial lesion, in 1925, he noticed that his hearing was becoming impaired, especially on the left, and that there was a weakness of the left side of the face. The facial weakness appeared quite suddenly—overnight, as he recalled—and persisted with no noticeable change. In 1926, he underwent a nasal operation and tonsillectomy, followed by a transient improvement in hearing. However, within a year's time, hearing was so affected that it became necessary for his friends to talk quite loudly in order to converse with him. There was no history of disease of the middle ear.

23. Winkelman, N.: Hyperostosis and Tumor Infiltration of Base of Skull Associated with Overlying Meningeal Fibroblastoma, Arch. Neurol. & Psychiat. **23**:494 (March) 1930.

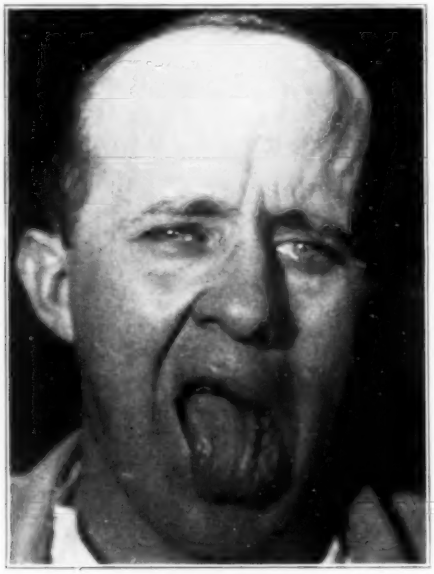

Fig. 1.—Front view of the patient, showing the bony swelling in the left frontal region, the weakness of the left corner of the mouth and the atrophy of the left side of the tongue.

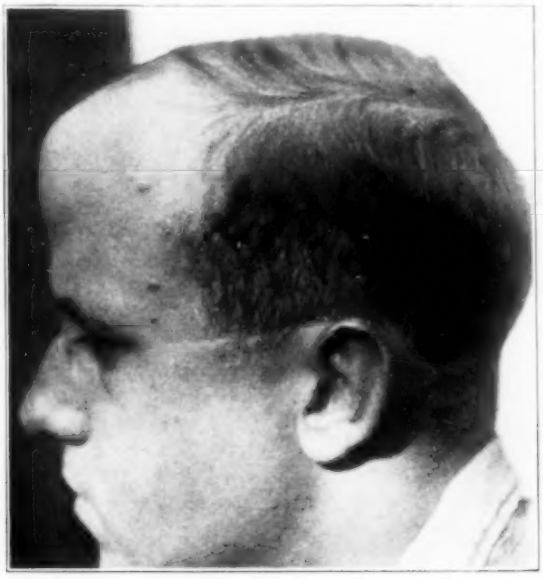

Fig. 2.—In this, the lateral, view can be seen more clearly the bony prominence in the left frontal bone.

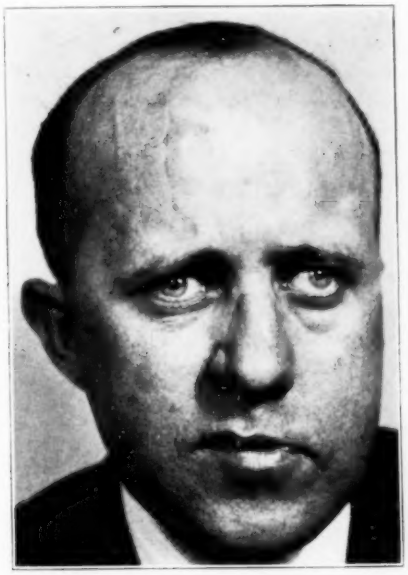

Fig. 3.—The well healed postoperative scar is clearly shown. The entire hyperostosis was removed with almost no deformity.

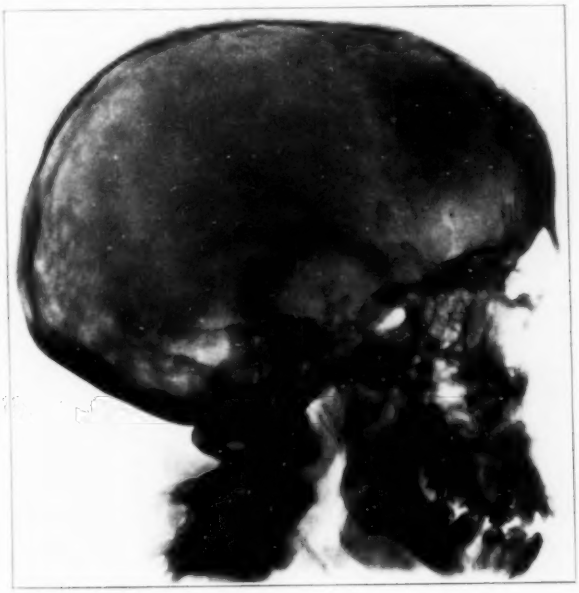

Fig. 4.—The bony thickening in the left frontal bone; it does not extend beyond the midline.

No additional symptoms were observed until 1927, when the patient experienced some difficulty in playing the piano. The fingers of the left hand could not be moved with the usual facility, and a weakness in extending the fingers and wrist of the same hand soon followed. This extensor weakness increased and was accompanied by an atrophy of the corresponding muscle group. He was unaware of the paralysis and atrophy of the left side of the tongue until his attention was called to the fact during the course of the examination. The duration of this symptom, therefore, could not be determined.

Physical Examination.—The patient was fairly well developed and of rather short stature. The interesting feature of the head was the bony tumor situated in

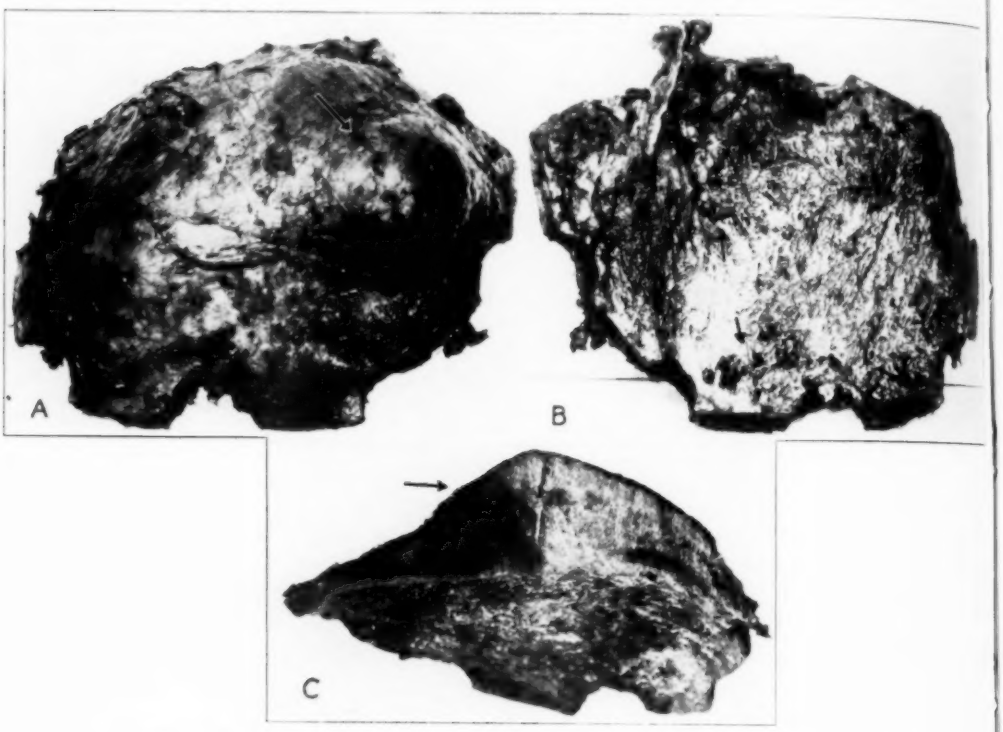

Fig. 5.—In *A*, indicated by the arrow, can be seen the soft pad of tissue lying over the area of hyperostosis. The numerous small hyperostoses on the inner side of the skull are seen in *B*. The relative proportion of soft and bony tissues is seen in *C*, the soft tissue being indicated by the arrow.

the left frontal region. It was not tender to palpation or percussion; it measured 8 cm. in diameter, projecting about 1.5 cm. above the normal contour of the skull. Roentgenograms showed a diffuse area of density of the bone, intermingled with rarefaction, which was most pronounced in the left frontal region, with no extension across the midline and extending posteriorly to involve the left parietal bone. A diagnosis of fibroblastoma was made.

The pupils were round and regular, the left slightly larger than the right, and reacted equally well to light, despite the presence of a large opacity in the posterior

capsule of the left lens and vitreous. Accommodation and convergence were impaired. A slight external strabismus of the left eye was noted, but without limiting ocular movements. The visual acuity of the left eye was 6/60, of the right, 6/22; the visual fields were full. Ophthalmoscopic examination of the right eye showed obliteration of the margin of the disk. The disk was gray, with poor vascularity,

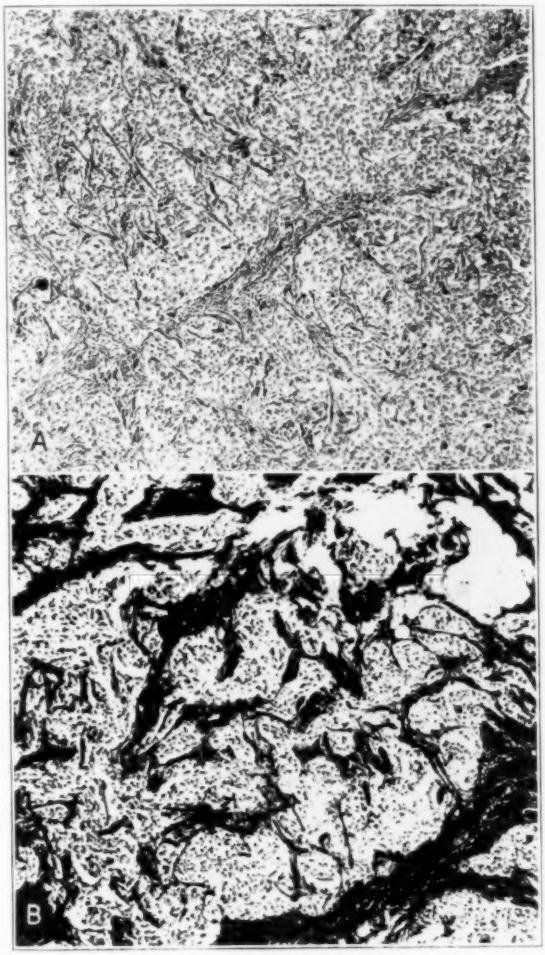

Fig. 6.—The fibroblastic nature of the tumor is evident in these photographs. In *B* can be seen the rich fibrous tissue stroma.

and had the appearance of a subsiding edema, a measurement of less than 1 diopter being obtained. An old retinal hemorrhage was undergoing absorption. The fundus of the left eye could not be seen.

The left facial weakness, of approximately five years' duration, was manifested by an inability to raise the left corner of the mouth to the same level as that of the right. It undoubtedly was of central type. Marked atrophy and fine fibrillary

tremors were noted of the left half of the tongue, which deviated to the left on protrusion. The reduction of auditory acuity was pronounced, especially on the left. Dr. Winston reported that the right ear-drum was somewhat retracted; the left was thickened and sclerotic. Bone conduction remained good in both ears, and it was concluded that the deafness was of an obstructive character. This was further substantiated by a Bárány examination, which showed, in addition, a total loss of vestibular function on both sides. The cerebellopontile angle and the cerebellum were said to be uninvolved.

Fig. 7.—At the edge of the skull can be seen the invasion of the bone by the tumor of the soft tissue. Small islands of tumor cells can be seen within the bone.

The other interesting feature of the examination was the rather marked extensor weakness of the left fingers and wrist. It was practically impossible for the patient to straighten out the fingers and the hand. Wasting of the extensor muscles of the forearm was pronounced, and the arm and shoulder girdle did not entirely escape. Flexor power was well preserved, the grip of the left hand recording 50 on the dynamometer, compared with 80 on the right. There was no abnormality in the gait and station. The deep tendon reflexes could not be obtained even with the aid of reinforcement. No pathologic reflexes were elicited.

A pressure of 220 mm., as recorded by the water manometer, was obtained on lumbar puncture. The fluid showed a moderate increase in cell count and protein content. The serologic and other laboratory studies gave entirely negative results.

Operation.—On Dec. 13, 1930, Dr. Frazier removed the bony tumor. There was found to be no dural attachment to the inner table. The latter was slightly roughened and showed increased vascular markings, but was otherwise normal in appearance. The dura was normal, and, when opened, an exploration of the cerebral cortex failed to reveal a fibroblastoma. No unusual tension of the brain was noted.

The patient made an uneventful and speedy convalescence, was out of bed on the fifth day, and was discharged on the tenth day. Although difficult of satisfactory explanation, auditory acuity was sharpened and power in extending the fingers

Fig. 8.—Within the bone large islands of tumor tissue such as this are not uncommon.

of the left hand and wrist was slightly improved. The other findings observed before operation persisted.

Pathologic Condition.—Gross Specimen: The frontal bone flap that was removed at the operation included the entire bony hyperostosis that was present in the left frontal bone. The entire specimen measured 10 cm. in length and 7 cm. in width. The hyperostosis consisted of a hillock-like swelling, the greatest bony thickening being in the center of the hyperostosis, shading off gradually as one approached the normal skull. The outer surface of the bony swelling was covered with a firm, fibrous layer of tissue which was about one-fourth inch (0.64 cm.) thick and firmly adherent to the outer table of the skull. The inner table was lined with a few hyperostoses. The bone on its cut surface had lost its diploe. It seemed com-

pressed and denser than normal. On the inner table of the skull also was a rather large swelling which, however, was not as prominent as that on the outer table. It is of interest to note that the soft tumor that lay on the outer table of the skull, when separated from the latter, could not be peeled away cleanly. It left a ragged surface of soft tissue penetrating the bone. No dura was removed.

Microscopic Examination: On the outer table of the skull, over the area of hyperostosis, was a firm, hard, dense cap of fibrous tumor substance. This tissue was composed of cells arranged in streams, or indistinct whorls. Among them was an extremely dense framework of fibrous tissue, which was spread in broad bands throughout the tumor. Fibroglia fibrils and elastic tissue were not found. Blood vessels were relatively numerous in the tumor. The type cell consisted of an element with an oval nucleus, a stout nuclear membrane, sparse and finely granular chromatin, a good nucleolus and an indistinct cytoplasm. The structure was that of a typical fibroblastic tumor, except that no well differentiated fibroglia fibrils could be demonstrated.

This tumor penetrated into the bone, extending along the haversian canals, and filling all the bone spaces with tumor cells. The latter had a structure in all respects similar to the cells in the soft tumor. No evidence of osteoblastic formation was seen anywhere in the bone. In some parts large areas of bone were entirely replaced by tumor cells. The bone was dense and typical in structure.

COMMENT

Our case presents two points of great interest: (1) the soft tumor lay on the outer surface of the skull and was associated with a hyperostosis beneath, and (2) there was a close association of trauma and persistent swelling in the area that was later the seat of trouble.

In none of the cases recorded have we encountered a tumor of the soft tissues of the scalp associated with an underlying bony swelling of the skull. It is well known, since the studies of Penfield, that the focus of greatest growth of the hyperostosis, in tumors within the cranium associated with bony enlargements, is at the apex of the tumor beneath the scalp. Here, too, proliferation of the bone is most active. The possibility, therefore, presents itself that we are dealing really with the soft tissue apex of a meningioma, rather than with a primary tumor of the soft tissues of the scalp. That this is not so is shown by the fact that the dura under the bone flap showed no evidence of tumor. The dura itself was not thickened, and exploration under the dura failed to reveal a tumor within the cranial vault.

The mere fact that the bony enlargement described in our case was associated with a tumor lying above it is not in itself a matter of great import. It is of some interest, however, that a localized hyperostosis need not necessarily be associated in every instance with a fibroblastoma of meningeal origin. That it has been reported as associated with the latter in practically all instances recorded is true. Furthermore, it is equally true that such localized hyperostoses may be caused in certain instances by fibroblastomas arising from the meninges. They may

rarely be due to other causes, however. In our case there was a fibroblastoma of the soft tissues of the scalp.

The occurrence of the hyperostosis in our case indicates that there is nothing specific in the production of localized hyperostoses by meningeal fibroblastomas. Apparently, fibroblastic tumors of any sort situated either over or under the skull are capable of causing localized bony growths. It is the fibroblastoma that possesses the peculiarity in question, rather than the fibroblastoma of meningeal origin specifically.

It has been believed by some (Brissaud and Léreboullet) that the tumor cells are capable of producing the bony enlargement, owing to some inherent power that they possess as tumor cells of meningeal origin. The studies of Penfield have shown that the tumor cells have no bone-forming capacity, and that the bone is produced by stimulation of osteoblasts to activity. That the hyperostosis is not produced by meningeal tumor cells that have assumed the capacity of forming bone is further indicated by our case, in which the tumor was not of meningeal origin, and yet in which the bony enlargement was similar in all respects to that seen in cases of meningeal fibroblastomas.

The relation of trauma to the hyperostoses and their associated tumors is intriguing. Spiller was the first to point out that trauma could be a factor in the production of these conditions. In 1907, and again in 1929, he asserted that trauma could be responsible for the bony enlargement, and that the soft tumor could follow on this. He reasoned that enlargement of the bone followed the trauma, and that the underlying tumor resulted from the constant irritation to the meninges of the hyperostosis. Spiller did not deny that in many cases the hyperostosis is with invasion of the bone by tumor cells, but most cases are examined late and it is not always possible to decide whether or not the enlargement of bone occurred before the bone was invaded by tumor cells. In support of his view he cited the case of Ashhurst, in which no tumor cells were found in the hyperostosis overlying the fibroblastoma. Spiller himself examined the bone. We have been able to find a similar case (Sternberg) in which an exostosis of the skull overlay a fibroblastoma, and in which no tumor cells were found in the bone. It is impossible to explain these few cases of bony enlargement without invasion by tumor cells on the basis of the theory of invasion by tumor cells. Nor can those cases of bony enlargement accompanied by scanty infiltration of the bone with tumor cells be explained satisfactorily on this basis. Trauma may account for the pathologic changes in some or even most of these doubtful cases.

Recently, Walshe [24] has agreed with Spiller that trauma may play a rôle in some cases of meningioma, and he quoted a case of Cushing [12]

24. Walshe, F. M. R.: Intracranial Tumors, Quart. J. Med. **96**:587 (July) 1931.

in which trauma and the meningioma were closely related. He related a further case of his own, that of a man who, sixteen years previously, had sustained a severe blow on the skull about one inch (2.5 cm.) to the left of the midline and 2 inches (5 cm.) behind the rolandic fissure. A trephine was performed at the time of the injury. The patient made a complete recovery and continued in good health until April, 1930, when a right hemiplegia developed suddenly. At postmortem examination, seven weeks later, there was found a large meningioma, under the bone defect from the old trephine, attached to the wall of the longitudinal sinus. Immediately above the tumor the bone was thickened and abnormally vascular, though the external prominence was present. Walshe stated that "it is impossible to escape the conviction that in these two cases we are dealing with a sequence of closely related events."

In our case, trauma seems to have played an important rôle. At 2 years of age, our patient fell against a hot stove, burning the left side of his forehead, and leaving a scar which has persisted. Five years before consulting a physician, he received an insignificant blow on the left side of the forehead, causing a swelling which did not recede, but which became progressively larger during the course of the next five years. In this case, therefore, trauma was closely related with a swelling of the affected part, a swelling that followed the trauma and never disappeared. Three alternatives come to mind: (1) following the trauma, fibroblasts in the subcutaneous tissue of the scalp were stimulated to the formation of a tumor; (2) fibroblasts, which were already overabundant in the region of the old scar from the trauma and burn at the age of 2 years, were stimulated to the formation of tumor by the added trauma of the second injury; (3) the trauma to the forehead was associated with a small hematoma, which later became organized and replaced by fibroblasts that were produced in great overabundance. Following the production of the soft tumor of the scalp, came invasion of the bone by the tumor cells and the production of a hyperostosis, after the manner described by Penfield, Cushing and others. It seems highly probable, therefore, that trauma was followed by a fibroblastoma, which may have been followed in turn by a hyperostosis caused by the invasion of the bone by tumor cells, but it is also possible that trauma *per se* caused the enlargement of the bone.

We do not believe that trauma is responsible for all the hyperostoses accompanying meningeal fibroblastomas. We believe, however, that trauma plays an important rôle in some cases, and our case seems to illustrate this point.

CHOLESTEROL CONTENT OF BLOOD IN EPILEPSY AND IN FEEBLEMINDEDNESS

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Fat metabolism in epilepsy merits intensive investigation because of:

1. The unappreciated frequency of paroxysmal disorders. These troubles include not only the grand mal of deteriorated patients in institutions, who are estimated at less than 4 per cent of all epileptic persons, but also the convulsive seizures that handicap a much larger number of afflicted persons in the community, and the still commoner, supposedly related psychic, vasomotor or irritative phenomena, such as migraine, visual disturbances and faint spells.

2. The success of treatment by a diet high in fat and low in carbohydrate.

3. The disagreement between reported fat values in the blood in epilepsy, some high and others low, as shown by the following tabulation:

High		Low	
Peritz	1909	Parhon, Urechia, Popea	1913
Pighini	1911	Pezzali	1923
Bornstein	1911	Popea and Vicol	1925
de Crinis	1920	Ornstein	1925
Targowla, Badonnel, Berman	1923	Robinson, Brain, Kay	1927
Goebel	1924	Goodall	1929
Claude, Targowla, Badonnel	1926	Gosden, Fox, Brain	1929
Jacobi	1927		

Lennox and Cobb's exhaustive monograph on epilepsy indicates that reconciliation of the discrepant observations is difficult because of uncertainty, either on the part of the author or on that of the reader, as to the time at which the blood was taken with relation to meals and to attacks, and because of the small number of persons from whom blood samples were analyzed, or the small number of the samples. Hence, series of determinations are necessary, either on the same person over a cycle of attacks and free intervals, or on a considerable group of persons, or on both. The last named was our aim.

From the Stanford University School of Medicine, San Francisco, and the Presbyterian Hospital, Chicago.

This work was done largely with the support of the Behavior Research Fund at the Institute for Juvenile Research, Chicago; series B, no. 180.

MATERIAL

All the patients were men above the age of 20, except for a few adolescent patients, who are specified. They were inmates at the State Hospital in Dixon, Ill. Authority to use this material and assistance were given by Dr. Warren G. Murray, the superintendent, and also Dr. H. B. Knowles and Dr. John F. Donahoe, who helped us in many ways.

For controls, we used adult workers at the Institute for Juvenile Research in Chicago.

METHODS

Taking of Blood Samples.—Specimens of blood, each amounting to about 10 cc., were drawn from the antecubital vein, with a tourniquet in place, into a syringe, and immediately shaken with a few crystals of potassium oxalate to prevent coagulation. Wide-mouthed bottles were used in order to admit Ostwald pipets. Convenient as carrying cases were aluminum egg boxes fitted with two dozen 2 ounce (59.1 cc.) bottles; the weight after loading was about 3 Kg.; they were occasionally mailed by parcel post at a cost of about 10 cents each, but were usually carried on an unenclosed platform of the train in order to avoid the heat inside the coaches.

The work was done between October 1 and April 30. Samples were taken from normal and feebleminded persons four hours after meals, and from epileptic persons as follows:

1. At first, at one, four and twelve hours after meals.

2. Later, at the following intervals after attacks, with omission of any patient known to have had a previous attack within one week: (*a*) within fifteen minutes; (*b*) one hour; (*c*) about from four to twelve hours, taken before a meal if possible; (*d*) about twenty-four hours, taken before a meal if possible; (*e*) about two days, taken before a meal if possible; (*f*) about three days, taken before a meal if possible; (*g*) about four days, taken before a meal if possible; (*h*) one month or more, taken before a meal if possible.

Sample Diet.—The diet of the epileptic patients may be illustrated by the following sample menu: Breakfast—cereal served with milk, bread and butter, syrup, bologna sausage or beef stew, coffee and milk or cocoa. Dinner—meat or stew, potatoes, corn or beans, cabbage, bread, pudding or raisin pie. Supper—vegetable soup, macaroni and cheese, or noodles, or lima beans, bread and butter, stewed peaches or apples, tea and cake and milk.

Cholesterol Analysis.—Bloor's method without saponification was used for determination of cholesterol. The reason for changing from Bloor's method with saponification, which had been used in our work on cholesterol in the blood of diabetic patients, reported in 1918 and 1924, was the knowledge that cholesterol gives the reaction as well while still in ester form as when free, and that one step in the process is thereby saved.

Whole Blood vs. Plasma.—The cholesterol values obtained for whole blood tend to be lower than those obtained for plasma, as can be seen in the low ratio of the cholesterol of whole blood to that of plasma (WB/Pl) in epileptic and in normal persons shown further on in this paper. For the most part, we have used whole blood rather than plasma because:

1. The amount of blood required from the patient needs to be only the volume chosen for putting into the alcohol-ether mixture for extraction, whereas to

extract the same volume of plasma, one must take twice this amount of blood. This consideration becomes of importance when use is made of serial samples.

2. The time and trouble of centrifugation are avoided.

3. There is scanty experimental backing for the frequent assumption that corpuscles resemble other cells with a fairly constant composition, and that therefore they act mainly as a diluent tending to mask changes in the plasma, in which the major changes supposedly occur; the evidence is equivocal especially with regard to such factors as absorption and membrane permeability.

4. Folin recently remarked: "Most of us probably have felt for years that it would be more satisfactory for nearly every purpose if the analyses could be based on blood plasma rather than on whole blood. . . . But in general, especially for clinical purposes . . . such a proposal is quite impractical."

STABILITY OF CHOLESTEROL IN OXALATED BLOOD

The question of the stability or lability of cholesterol value in oxalated blood on standing for a day or more before extraction with

TABLE 1.—*Changes in Cholesterol Value of Plasma After Standing Forty-Eight Hours*

Change	Amount of Change in Gm. per 100 Cc., and Number of Pairs* Showing Given Amount of Change				Total Number of Pairs Showing Change
	0.00	0.01	0.02	0.03	
Second value above initial value..	0	10	4	3	17
Second value below initial value...	0	0	0	0	0
No change	3	0	0	0	3
Total number of pairs showing given amount of change.....	3	10	4	3	20

* Pair refers to value of portion of sample extracted at four hours and value of portion extracted at forty-eight hours.

alcohol-ether mixture arose because the distance from the Dixon State Hospital to the laboratory resulted in an interval between the taking of the blood and the extraction with alcohol-ether mixture, which amounted to three or four hours when one of us made the trip, and to more than twenty-four hours when the samples of blood were mailed.

As evidence, we may use the difference between a pair of values on each blood, one that of the usual extract made on a portion within four hours and the other that of the extract of a portion after it had been allowed to stand for a period varying from forty-eight hours to twenty-five days. This difference is tabulated in table 1, and may be summarized thus:

In plasma, after separation and standing for forty-eight hours (table 1), the average change was an increase of cholesterol by 0.013 Gm., or 13 mg., per hundred cubic centimeters of plasma. This change seems negligible for our purposes.

In plasma, after it had stood about ninety-six hours (table 2), the average change was a rise of 0.007 Gm., or 7 mg., per hundred cubic

centimeters. This is negligible for our purposes. However, we may record these additional observations:

1. Among seven samples of blood that were tested three times (initially, at forty-eight hours and at ninety-six hours), four samples in which the extraction at forty-eight hours had shown some increase above the initial value, at ninety-six hours showed a slight further rise, while the other three samples that showed a rise at forty-eight hours did not rise further at ninety-six hours.

2. The two samples that showed a ninety-six hour value below that obtained in the initial test were found to have been noted on receipt as hemolyzed. We conclude that hemolyzed samples should be discarded.

TABLE 2.—*Changes in Cholesterol Value of Plasma After Standing Four Days*

Change	Amount of Change in Gm. per 100 Cc., and Number of Pairs Showing Given Amount of Change								Total Number of Pairs Showing Change
	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	
Above first value	0	3	5	2	0	0	0	0	10
Below first value	0	0	0	1	0	0	0	1	2
No change	1	0	0	0	0	0	0	0	1
Total number of pairs showing given amount of change	1	3	5	3	0	0	0	1	13

TABLE 3.—*Changes in Cholesterol Value of Whole Blood After Standing a Week*

Change	Amount of Change in Gm. per 100 Cc., and Number of Pairs Showing Given Amount of Change			Total Number of Pairs Showing Change
	0.00	0.01	0.02	
Above first value	0	6	0	6
Below first value	0	10	3	13
No change	37	0	0	37
Total number of pairs showing given amount of change	37	16	3	56

In whole blood that had stood a week (table 3), the average change was a decrease of 0.0018 Gm., or approximately 2 mg. per hundred cubic centimeters. This is negligible for our purposes. Furthermore, among the thirty-seven samples showing no change were four samples that had stood twenty-one days (three weeks).

Cholesterol is sufficiently stable to permit the use of samples of oxalated plasma that has stood four days, or of whole blood that has stood a week (and probably even of that which has stood three weeks).

CONSTANCY OF CHOLESTEROL CONTENT IN BLOOD OF EACH PERSON

The constancy of the cholesterol content in the blood of a person at different times after taking food, not necessarily on the same day, may be examined by comparing specimens drawn:

1. All at the same interval after eating, the cholesterol values at the following intervals being compared:

(*a*) One hour after eating (range from 1 to 2 hours after food).

(*b*) Four hours after eating (range from 3 to 5 hours after food).

(*c*) Twelve hours after eating (range from 8 to 14 hours after food).

2. At different intervals, the cholesterol value at the earlier period being compared with that at the later:

(*a*) One and twelve hours after eating.

(*b*) Four and twelve hours after eating.

(*c*) One and four hours after eating.

(*d*) One hour, four hours and twelve hours after eating.

TABLE 4.—*Constancy of Value for Blood Cholesterol in Two Successive Samples from Each Person at Same Interval After Eating: Frequencies*

Hours After Eating	Amount of Change in Gm. per 100 Cc., and Number of Pairs Showing Given Amount of Change							Total Number of Pairs for Given Interest
	0.00	0.01	0.02	0.03	0.04	0.05	0.06	
1	12	23	20	6	6	0	0	67
4	37	76	34	11	5	1	1	165
12	13	20	11	5	1	1	1	52

TABLE 5.—*Constancy of Value for Blood Cholesterol in Two Successive Samples from Each Person at Same Interval After Eating: Averages*

Hours After Eating	Average Difference, Gm. per 100 Cc.	Proportion of Pairs to Show Difference of 0.03 Gm. or Less per 100 Cc.
1	0.016	61/ 67, i.e. 91%
2	0.012	158/165, i.e. 96%
12	0.014	49/ 52, i.e. 94%

The amount of variation in a patient at the same interval after meals is shown in tables 4 and 5. The inferences we draw are that the cholesterol level in the identical person at the identical interval after eating varies up to 30 mg., and that therefore a difference between two cholesterol determinations must be at least 40 mg. before that difference should be given much consideration. In order to interpret differences of 30 mg. or less, the observer should apparently have either serial cholesterol measurements on one person or single measurements on a group of persons.

The data obtained at the several intervals after meals may be compressed into tables 6 and 7. The conclusions again are that most of the differences (in from 92 to 96 per cent of the pairs) are 300 mg. or less, and accordingly that such differences should be regarded as within the normal range of variation of the individual.

Some further details may be indicated. Determinations at all three times (one, four and twelve hours after eating) were made in thirty patients (table 8). In these, we notice that the value one hour after eating was the highest of the three determinations more than half the time. Or again, when we search for values at twelve hours after eating

TABLE 6.—*Constancy of Value for Blood Cholesterol in Samples from Same Person at Different Intervals After Eating: Frequencies*

Hours After Eating	Difference Between Samples	Amount of Change in Gm. per 100 Cc., and Number of Pairs Showing Given Amount of Change						Total Number of Pairs Given Difference
		0.00	0.01	0.02	0.03	0.04	0.05	
1 and 12	12 hours, larger	0	7	3	1	0	0	11
	12 hours, less	0	11	2	2	3	0	18
	Both alike	9	0	0	0	0	0	9
	Total	9	18	5	3	3	0	38
4 and 12	12 hours, higher	0	7	1	0	0	0	8
	12 hours, lower	0	10	3	2	2	0	17
	Both alike	18	0	0	0	0	0	18
	Total	18	17	4	2	2	0	43
1 and 4	4 hours, greater	0	31	5	3	1	0	40
	4 hours, smaller	0	26	8	1	2	1	38
	Both alike	35	0	0	0	0	0	35
	Total	35	57	13	4	3	1	113

TABLE 7.—*Constancy of Value for Blood Cholesterol in Samples from Same Person at Different Intervals After Eating: Averages*

Hours After Eating	Difference Between Samples, with Amount of Difference in Gm. per 100 Cc.	Percentage of Pairs to Show Difference of 0.03 Gm. or Less per 100 Cc.
12 and 1	12 hours less by 0.004	92
12 and 4	12 hours less by 0.009	95
1 and 4	1 hour less by 0.009	96

TABLE 8.—*Constancy of Value for Blood Cholesterol in Samples from Patients One Hour After Eating: Frequencies*

Value	Number of Times	Percentage of Times
Highest	16	53.3
Lowest	11	36.6
Medium	1	3.3
Equal	2	6.7
Total	30	99.9

(fasting) and also at one of the earlier periods, we find records on fifty-six patients (table 9). In them, the blood during fasting had, surprisingly enough, the lowest value in only about 45 per cent, i. e., by no means in all. From this we deduce that meals, in this institution at least, affected the cholesterol level in the blood to only a moderate degree, and irregularly, so that results at different intervals after meals may fairly be pooled, at least for treatment of observations in the mass.

AVERAGES BASED ON BLOOD SAMPLES AS COMPARED WITH THOSE BASED ON PERSONS

The averages obtained by taking a sample from each person only once may be compared with the averages obtained by using all the samples of blood. A theoretical objection to the use of all the samples is that multiple samples from certain persons "weight" those persons, and if they happen to be remarkable may depress or raise the averages. On the other hand, the argument for using all the determinations is partly that it is convenient and partly that there is an advantage in having as large a series as possible in order to permit subdivision and to decrease

TABLE 9.—*Constancy of Value for Blood Cholesterol in Samples from Patients Twelve Hours After Eating: Frequencies*

Value	Number of Times	Percentage of Times
Lowest	25	44.7
Highest	18	32.2
Medium	2	3.6
Equal	11	19.7
Total	56	100.2

TABLE 10.—*Average Values of Blood Cholesterol Based on Persons as Compared with Those Based on Blood Samples*

	Patients		Samples	
Hours After Eating	Number of Tests	Mg. per 100 Cc. ± Probable Error	Number of Tests	Mg. per 100 Cc. ± Probable Error
Whole blood				
1	122	168 ± 1.2	189	168 ± 1.1
4	149	167 ± 1.2	312	163 ± 0.8
12	67	167 ± 1.8	122	166 ± 1.3
All hours pooled	338	168 ± 0.8	623	165 ± 0.6
Plasma				
1	8	169 ± 7	14	173 ± 7
4	25	196 ± 5	48	187 ± 4
12	0		0	

the probable error. If now both methods are applied to the determination of the blood cholesterol in epileptic persons, we get table 10. We conclude that the difference between persons and samples, i. e., between the pair of means in the two columns in the table, is mathematically significant only for whole blood at four hours after eating, and even then is not impressively marked. In the absence of striking differences, accordingly, we shall in the rest of this paper base our averages on samples rather than on persons.

EFFECT OF RACE

As there were a number of Negroes among our patients, it seemed worth while to determine whether race affected the cholesterol values. The largest proportion of the Negroes on whom we had records hap-

pened to be in the group of 108 feebleminded persons; so we examined this series. In the 90 white persons, the whole blood cholesterol averaged 154 ± 1 mg. per hundred cubic centimeters, whereas in the 18 Negroes it averaged 156 mg. per hundred cubic centimeters. The difference was not significant, and therefore we consolidated our observations irrespective of race.

EFFECT OF AGE

As a number of our patients were between 15 and 20 years of age, it seemed desirable to measure the differences in cholesterol content of the blood that might be due to adolescence. The data on whole blood were examined. Among the feebleminded persons, the 60 adults (i. e., aged 20 or more) averaged 153 mg. per hundred cubic centimeters, with a probable error of 1.5 mg., while the 48 adolescents averaged 155 ± 1.7 mg.; similarly, among the epileptic patients, the 623 adults averaged 164.9 ± 1 mg. per hundred cubic centimeters (range from 115 to 235), whereas the 11 adolescents averaged 149.1 mg. per hundred cubic centimeters (range from 120 to 178). It is seen that the adolescents had a slightly higher cholesterol level than the adults among the feebleminded persons, while among the epileptic patients the reverse was found; i. e., the adolescents had the lower level and a markedly lower level; hence the evidence was not final. We decided to pool the results for the adolescents in our epileptic series with those for the adults, especially because the blood samples of the adolescents amounted to only 1.8 per cent of those of the epileptic persons.

CHOLESTEROL CONTENT AND DIAGNOSIS

For normal persons we established our own standards by running determinations on a certain number of controls, following the advice of various workers, and found that, although all the determinations were done by Bloor's method, by one with extensive training in biochemistry (Dr. McGee), our norms differ significantly from Bloor's, being lower. The frequency distribution and constants for our 29 normal, 108 feebleminded and 623 epileptic persons are shown in table 11, and a condensed summary in table 12. The conclusions are outspoken: The average concentration of cholesterol in the blood of epileptic persons was lower than that in the blood of normal persons, and significantly so. The average in feebleminded persons was even lower than that in epileptic persons.

EFFECT OF FOOD

For our purposes, and probably for most practical purposes, existing evidence that blood cholesterol can be elevated after forced fat feeding is not pertinent. The question concerns the effect of ordinary meals of

mixed foods. The averages, as shown in table 13, were higher at one hour after eating, and lowest at four hours; the difference is significant. The value during fasting (i. e., twelve hours after meals) is surprising in being actually higher than at four hours after eating, but the margin

TABLE 11.—*Cholesterol in Whole Blood in Our Normal, Feebleminded and Epileptic Series: Frequency Distributions, Means ± Probable Errors, Standard Deviations, Coefficients of Variability*

	Normal Persons 4 Hr. After Food	Feebleminded Persons 4 Hr. After Food	Epileptic Persons							
			1 Hour After Food		4 Hours After Food		12 Hours After Food		All Hours After Food	
Mg. per 100 Cc.			Persons	Samples	Persons	Samples	Persons	Samples	Persons	Samples
115-124	...	2	1	5	2	6	1	1	4	12
125-134	...	10	5	9	6	22	3	6	14	37
135-144	...	23	8	14	13	30	4	12	25	56
145-154	...	25	19	29	25	68	12	21	56	118
155-164	3	26	25	38	33	59	17	30	75	127
165-174	4	12	23	32	21	48	10	18	54	98
175-184	5	4	15	19	12	21	5	10	32	50
185-194	3	5	11	29	21	28	5	9	37	57
195-204	2	...	6	7	9	17	5	7	20	31
205-214	8	...	7	9	3	8	3	6	13	23
215-224	1	...	2	6	3	4	2	2	7	12
225-234	3	1	...	1	1	1	...	...	1	2
Total number	29	108	122	189	149	312	67	122	338	623
Mean, mg. per 100 cc.	194	154	168	168	167	163	167	166	168	165
Probable error of mean	2.7	1.1	1.3	1.1	1.2	0.8	1.8	1.3	0.8	0.6
Standard deviation	22	17	21	23	22	22	22	22	22	22
CV = 100 SD/M	11.5	11.2	12.6	13.3	13.2	13.5	22.2	21.5	21.6	22.2

TABLE 12.—*Comparison of Average Amounts of Cholesterol in Blood of Normal, Feebleminded and Epileptic Persons Four Hours After Eating*

	Average Amount of Cholesterol, Mg. per 100 Cc.		
Diagnosis	Whole Blood	Plasma	Whole Blood/Plasma
Normal	(29) 194 ± 2.7	(20) 216 ± 6.4	(20) 91 ± 1.9
Feebleminded	(108) 154 ± 1.1	(16) 148 ± 3.9	(15) 102 ± 1.2
Epileptic	(623) 165 ± 0.6	(48) 187 ± 3.7	(43) 93 ± 1.0

TABLE 13.—*Effect of Food on Cholesterol in Blood of Epileptic Patients*

	Amount of Cholesterol, Mg. per 100 Cc.		
Hours After Eating	Whole Blood	Plasma	Whole Blood/Plasma
1	(189) 168 ± 1.1	(14) 173 ± 7.3	(14) 98 ± 1.0
4	(312) 163 ± 0.8	(48) 187 ± 3.7	(43) 93 ± 1.0
12	(122) 166 ± 1.3		
All pooled	(623) 165 ± 0.6		

is not significant; also it is strikingly close to the average for all the samples pooled. Remembering the great frequency, already shown, of variations of 30 mg. in the same person at the same hour after eating, we draw these inferences:

1. Food is followed at one or two hours by a rise in the blood cholesterol, and therefore the interval should be recorded.

2. Food frequently cannot be allowed for, owing to the wideness of personal fluctuation.

3. Mass values—trusting to balancing of food effects—are more likely to reveal the effect of whatever factor is being studied than are curves of serial samples on single patients.

4. The low cholesterol in the institutional patients, and the moderate amount of increase after meals, may have been partly due to the low fat in the diet, which may be noted in the sample diet list given earlier in this paper, as indeed in the diet of many institutions. To answer this question, it was planned to estimate cholesterol in a group of these patients after they had been transferred to high fat diets, but unfortunately this proved not feasible.

EFFECT OF SEIZURES

Average Cholesterol Content of Whole Blood.—Just as our samples (regardless of relation to attacks) were grouped by hours after eating in order to study the effect of food, so the samples were pooled irrespective of meals in order to examine the effect of convulsive seizures. The averages in table 14 show:

TABLE 14.—*Epileptic Seizures and Average Amount of Cholesterol in Whole Blood*

Interval Following Fit	Range of Interval	Number of Samples	Mean Cholesterol Content, Mg. per 100 Cc.
1 hour	1-2 hr.	179	162 ± 1.1
1 day	2-24 hr.	131	168 ± 1.2
1 day but less than 1 week	24-168 hr.	137	168 ± 1.3
1 week and less than 1 month	168 hr.-1 mo.	106	164 ± 1.6
More than 1 month	.....	70	172 ± 1.9
All intervals pooled	.....	623	165 ± 0.6

1. Within one hour following an epileptic fit, the cholesterol average reached a low point that was mathematically significant (162 mg.). These results confirm the striking findings of Robinson, Brain and Kay.

2. At intervals of from two hours to one week following a fit, the mean cholesterol was slightly higher than during the first hour.

3. At intervals of between one and four weeks following a fit, the cholesterol average was slightly lower again. After verifying the correctness of the calculation of this mean, and on considering the difference together with the probable error of that difference, 4 ± 2.3 mg. per hundred cubic centimeters, we conclude that the drop was not statistically significant.

4. At intervals of more than one month after seizures, the mean cholesterol had risen significantly to 172 mg. Even then the value was still significantly less than the mean cholesterol value of 190 mg. in our normal controls.

Ratio of Whole Blood Cholesterol to Plasma Cholesterol.—Table 15 suggests that near a crisis the ratio of whole blood cholesterol to plasma cholesterol is higher than at the intervals farther from the convulsion. The cause of the rise is due to increase of cholesterol in the whole blood, as just shown; whether the plasma cholesterol is decreased simultaneously we cannot say.

Serial Determinations of Cholesterol in Individual Patients.—There were a number of patients from each of whom a sample of blood was secured within two hours following a fit, and one or more samples later; indeed, from some patients we got several sets. The series has been tabulated in three groups showing, respectively, a drop near the fit, a rise, and no change. The long table is omitted, but may be summarized thus: Series low or lower at fit, 38; series high or higher at fit, 6; series unchanged at fit, 2. Some patients yielded high series at one time, low

TABLE 15.—*Epileptic Seizures and Mean Ratio of Cholesterol of Whole Blood to That of Plasma*

Interval Following Fit	Number of Samples	Whole Blood to Plasma Ratio, Average
1 hour	1	107
2 hours to 1 day	16	95
1 day to 1 week	14	99
1 week to 1 month	12	91
More than 1 month	14	91

at another; no satisfactory explanation is apparent. Some of the irregular low values are no doubt to the failure of patients to report attacks, a common concealment. On the whole, since 38 of the 46 series were low at the attack, this serial evidence seems to us important support of the evidence already given to show the effect of seizures.

SUMMARY

Patients and Controls.—Cholesterol was determined by Bloor's method in 623 samples of blood from epileptic persons, in 108 from feebleminded persons and in 29 from normal persons.

Stability of Cholesterol on Standing.—Cholesterol is relatively stable when oxalated blood is allowed to stand before extraction. Plasma was kept about ninety-six hours (four days), with negligible rise in cholesterol value compared with the value on the same plasma extracted immediately on receipt. Whole blood when kept forty-eight hours before extraction showed an immaterial increase of cholesterol, and when kept a week showed an average decrease, but as with the increase shown by the forty-eight hour test, the amount of decrease was so slight as to be negligible for practical purposes.

Whole Blood as Compared with Plasma.—The former was preferred. The reasons are given.

Cholesterol Constancy of Each Person.—At the same interval after eating, in two successive samples of blood, the difference in cholesterol content so frequently ran up to 30 mg. per hundred cubic centimeters that we judge that a difference in the cholesterol content of the blood of a person should be ignored unless it amounts to 40 mg. or more.

Effect of Food.—There is a rise in cholesterol in from one to two hours after eating, but the differences between the level shortly after meals and that overnight again are mostly within 30 mg., which we hold to be the range of error of the method in clinical use. We conclude that the effect of meals, while worth consideration in some studies, may be neglected in our project, and probably in most.

The use of *more than one sample* of blood from some patients, though open to statistical objection, is defended.

Effect of Race.—Negroes showed cholesterol values not significantly different from those shown by white persons.

Effect of Age.—In persons under 20, the cholesterol was higher than in adults among the feebleminded, but lower than in adults among the epileptic. This incongruity we attribute to the smallness of the series.

Cholesterol Content and Diagnosis.—The average cholesterol value of whole blood from men was, in normal persons, 194 mg. per hundred cubic centimeters; in epileptic persons, 165 mg., and in feebleminded persons, 154 mg. per hundred cubic centimeters.

Effect of Seizures.—Convulsions were followed in about one hour by a drop in cholesterol, and thereafter by a gradual rise, extending over perhaps a month, if no further attack occurred, but still not reaching the average value for normal men. The question may be raised: The greatest difference is only 10 mg. (172 mg. at more than one month as compared with 162 mg. at one hour), while the error of the method was estimated at 30 mg. Is the difference significant? The answer is that the error of 30 mg. referred to single observations; but in discussing convulsions we are dealing with means, and with means the observations counterbalance, and furthermore the difference of 10 mg. between means is significant in the light of the probable errors tabled.

Ratio Between Cholesterol in Whole Blood and That in Plasma.—Near an attack the ratio was increased, owing presumably to more cholesterol in the corpuscles and less in the plasma.

Treatment by High Fat Diets.—This method of treatment, which has been so favorably reported on by practical men, received support from

this laboratory evidence that cholesterol in epilepsy is low. The even lower cholesterol in the feebleminded patients indicates the possible utility of diets high in fat in institutions for the feebleminded.

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EXTRAMURAL PATIENTS WITH EPILEPSY

WITH SPECIAL REFERENCE TO THE FREQUENT ABSENCE OF DETERIORATION

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Descriptions of epilepsy in the literature are based almost entirely on studies of institutional cases. Writers of textbooks and monographs naturally found epileptic patients in institutions most convenient for study. Here there are concentrated large numbers of persons with epilepsy; their observation is rendered comparatively easy because many patients and records are available at the same time and place, and owing to the conditions necessary on confinement the same patients are available for study over a long period of time. It must be remembered, however, that most persons with epilepsy are sent to institutions not merely because they are epileptic, but because they have developed mental disturbances that make incarceration imperative. Since writers on epilepsy studied the disease in patients accessible to them because of mental changes, it is easy to understand why they all considered mental deterioration so common and so integral a part of the disease. There are, however, many persons with epilepsy who never reach an institution; they are seen only in private practice, and a study of these patients, as I shall try to show, gives one an entirely different view of the frequency of deterioration. I am convinced that mental changes in epilepsy are not nearly as frequent as the writers of textbooks and monographs lead one to believe, and I shall attempt to show that many persons, although afflicted with epilepsy for many years, carry their share of the world's burden and carry it well.

That mental changes usually occur in epilepsy has been stated by writers old and recent. In 1838, Esquirol [1] wrote that four fifths of the epileptic women in the Salpêtrière were insane, and that of 385 persons with epilepsy in Charenton 46 were hysterical, 12 monomaniacs, 30 maniacs, 34 furious, 145 demented and 50 reasonable but afflicted with loss of memory, and that 60 exhibted no aberration of intelligence. Hence, four fifths were more or less mentally deranged and one fifth

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preserved their reason, "but," Esquirol added, "what reason!" Morel [2] said that "it [epilepsy] exerts a peculiar influence on the psychic and moral personality."

Romberg [3] wrote that in persons with epilepsy it is characteristic to find loss of memory and diminution of the distinctness of ideas combined with great irritability of temper. Hasse [4] stated that the personality of the epileptic patient becomes more and more like that of a beast. Reynolds,[5] in a study of 62 patients, found 61.3 per cent deteriorated. Delasiauve [6] claimed that one is never safe in the presence of an epileptic patient. Echeverria [7] found that of 306 persons with epilepsy 118 were psychotic, but he added that circumstances prevented him from estimating without fallacy the degree of mental failure in this disease. Echeverria was in no doubt, however, about the moral status of the person with epilepsy, for he stated:

> Epilepsy contrasts singularly with other diseases in the deep mark it impresses on the organic and moral constitution of the individual. . . . Epilepsy leads to depravity . . . the fact evinces itself whether we look at the victim of the disease in any of the social ranks. The change is undergone more rapidly by him who breathes an atmosphere of vice than by him who does not. . . . In the first instance the patient becomes irritable and overbearing, a liar, addicted to masturbation or other wicked habits; whereas in the second case the seed sown in abundance yields a more pernicious fruit and drunkenness, larceny, arson, murder or crime in its most hideous conceptions lead the victim by counted steps to the gallows.

Gowers [8] stated that the mental state of persons with epilepsy frequently presents deterioration. Spratling [9] was of the opinion that from 8 to 10 per cent of epileptic patients may be called sane, within both the legal and the scientific sense. Liepmann [10] wrote that three fourths of these persons become insane, and Siemerling [11] placed this number at

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four fifths. Kraft-Ebbing [12] said that in the majority of cases of epilepsy the psychic functions are lastingly disturbed. Habermaas [13] thought that 13 per cent of persons with epilepsy were sane, and Bratz [14] found psychoses in all but 15.8 per cent. Turner [15] found that 13.6 per cent of epileptic patients do not deteriorate. Savage [16] contended that the natural sequel of many and frequent epileptic fits is some degree of mental enfeeblement. Starr,[17] from a study of patients in outpatient clinic and private practice, concluded that 10 per cent of persons with epilepsy become insane, but this writer did not state how long he followed his cases. Kraepelin [18] stated: "There usually develops with genuine epilepsy a more or less pronounced peculiar change in the personality, but in spite of the high degree of mental weakness, the behavior remains orderly."

Dercum [19] wrote that there are persons with epilepsy who in the intervals between the seizures are entirely normal and are able to follow their vocations fairly well, but there are others, and by far the greater number, who present both emotional irritability and mental impairment. Diefendorf [20] was convinced that epilepsy produces some mental deterioration in every case. Bleuler [21] thought that persons with epilepsy, as a rule, are psychopathic even before the disease has left its characteristic mark on them, but that specific psychic peculiarities are connected with epilepsy which, as a rule, increase with the duration of the disease. Pilcz [22] said: "Aside from unusually rare exceptions, a long-existing epilepsy generally results in certain permanent psychic anomalies that are often so pronounced that a diagnosis can be based on them."

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Muskens [23] believed that mental changes are nearly always associated with a persistence of epileptic fits. This writer further stated that a person with epilepsy is a source of danger to himself, his immediate surroundings and society as a whole. Henderson and Gillespie [24] stated that mental symptoms are generally found in cases of confirmed epilepsy, and Strecker and Ebaugh [25] wrote that while not every epileptic person becomes definitely insane, it may be accepted that he is scarcely ever normal.

The material used in this study consists of the records of 304 persons with epilepsy, from the private practice of Dr. Hugh T. Patrick, who have had the disease for six years or more. Although there were about 1,000 cases in the entire series, those patients who were afflicted for less than six years were not accepted for this study because it was thought that not enough time had elapsed for deterioration to begin. Ninety-nine, or 32.8 per cent, had been afflicted for from six to ten years; 75, or 24.6 per cent, for from eleven to fifteen years; 52, or 16.7 per cent, for from sixteen to twenty years; 31, or 10.2 per cent, for from twenty-one to twenty-five years, and 47, or 15.4 per cent, over twenty-five years. In many instances the patients had had the disease for the designated number of years when they were last seen; in 112 instances, although the patients had not been seen for several years, their present condition was determined by answers to a questionnaire. In this series only 20 patients, or 6.5 per cent, were found to be mentally deteriorated; some of these were in institutions. The remainder, or 93.5 per cent, were found to be in excellent mental health, without the slightest trace of deterioration or other psychosis, and engaged in occupations similar to those of the great mass of the population. In order that this question may not be dismissed with a bare statistical statement, I have prepared a table (table 1) showing in the first two columns the number of patients afflicted for a given number of years; in the next column the occupations that these patients were engaged in, and in the last column the number of deteriorated patients in each age group. Such a table is of interest in that it shows that most of the patients, regardless of how long they have had epilepsy, are still engaged in ordinary pursuits and some even in superior callings. Furthermore, if deterioration does occur, one would expect such a table to show a progressive vocational decline with a longer duration of the disorder; this the table does not show.

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TABLE 1.—*Data on Deterioration in Present Series*

Years Since Onset	Number of Cases	Occupation	Number of Deteriorated Patients
6	22	Teacher, grammar school pupil (2), farmer, manufacturer, seamstress, real estate dealer, high school student (8), lumber dealer, housekeeper (4), mechanic	1
7	29	Printer, dentist, lawyer, office work (3), clerk (2), teamster, machinist, farmer (2), college student (3), stenographer, housekeeper (6), linotype operator, dental student, postmaster, foreman of labor gang, idle, not stated (1)	1
8	18	Miner, farmer (2), housekeeper (4), college student (4), drug clerk, domestic, high school student (3), electrical engineer, bond salesman	0
9	12	Law student, grammar school pupil (3), bellboy, traveling salesman, pastor, college student (2), housekeeper (2), not stated (1)	0
10	18	Grammar school pupil, high school student (3), college student (2), practicing physician (2), storekeeper, housekeeper (2), bookkeeper, farmer (2), druggist, salesman, compositor, not stated (1)	0
11	24	Housekeeper (3), salesman, farmer, librarian, secretary, office worker, laborer, high school student, insurance agent, electrical engineer (2), merchant, farmer, preacher, grocer, draughtsman, contractor, law student, not stated (3)	1
12	14	Auto dealer, farmer, laborer (2), salesman, housekeeper, schoolboy, butcher, collector, clerk	4
13	7	College student, housekeeper (2), high school student, stenographer, not stated (2)	0
14	14	Advertising agent, manufacturer, farmer, housekeeper (2), contractor, musician, teamster, clerk, teacher, practicing physician, minister, not stated (1)	1
15	16	Nun, stenographer, housekeeper (2), lawyer (2), restaurateur, electrician, minister, law student, teacher, merchant, not stated (2)	2
16	16	Stockroom superintendent, seamstress, laborer, office worker, bank cashier, housekeeper, storekeeper, salesman, beauty parlor operator (2), editor and publisher, accountant, clerk, not stated (2)	1
17	8	Machinist, shipping clerk, housekeeper (3), news agent, teacher	1
18	9	Lawyer, teacher (2), farmer (2), college student, high school student, architectural engineer in practice	1
19	6	Farmer, housekeeper (2), postmaster, hospital intern, not stated (1)	0
20	13	Housekeeper (4), mail carrier, farmer, bookkeeper, salesman (2), milkman, bank cashier, not stated (1)	1
21	8	Housekeeper (4), office clerk, farmer, not stated	1
22	5	Office work, farmer (2), lawyer, mechanic	0
23	4	Compositor, cabinet maker, insurance agent, unlocated college graduate	0
24	8	Housekeeper (2), lawyer, salesman, insurance agent, farmer, journalist, piano teacher	0
25	6	Secretary, housekeeper (2), fisherman, Christian science practitioner, not stated (1)	0
26-30	21	Salesman, missionary, physician, stock dealer, housekeeper (4), furniture dealer and undertaker, manufacturer, addressograph operator, manager of store, factory foreman, lumber dealer, farmer (2), minister, not stated (1)	3
31-35	15	Accountant, bookkeeper, railroad station agent, farmer (2), housekeeper (4), farmer, banker, dentist, laborer, not stated (1)	1
36-40	5	Housekeeper (3), retired merchant, manufacturer	0
Over 40	6	Practicing physician, retired housekeeper, bank president, housekeeper (2)	1

In order to show the type of case dealt with here even more clearly than by a table, it is thought that a description of a few examples would be instructive and of interest.

REPORT OF CASES

CASE 1.—A. W., aged 63, stated that his father had had migraine, a paternal cousin had had epilepsy, and a maternal aunt had had migraine. Since the age of 5 (i. e., for fifty-eight years) he has had attacks in which he would suddenly get a "homesick" feeling with an indescribable dreamy state and discomfort around the lower part of the chest. The attacks were at times accompanied by obscuration of consciousness, and at other times followed by total loss of consciousness for several minutes. The frequency of the attacks varied from several per day to one per week or per month. From the age of 22 to 25, while the patient was under treatment, there were no attacks; since then he has had attacks continuously. He was given bromides, but did not adhere to the prescribed regimen. Instead, he treated himself with patent medicines and phenobarbital, with no effect on the attacks. When first seen, he was 42 years of age; in spite of the fact that he had had epileptic attacks for thirty-seven years, he was a bank president; in 1931, after having had epilepsy for fifty-eight years, with attacks coming regularly, he was still a bank president, and it may be added pertinently that the bank was still doing business.

CASE 2.—Miss H. G., aged 65, was first seen on Oct. 22, 1928. The mother had been "nervous" and "highstrung" and had had migraine. A brother was nervous and migrainous. The family history was otherwise negative for nervous and mental disorders. Thirty-one years before this writing, the patient began to have attacks which started with a yell and were accompanied by unconsciousness; during the seizures the face became bluish, and a short tonic and clonic convulsion occurred, accompanied by the passage of urine and biting of the tongue. Following the attacks, the patient slept for about fifteen minutes. The attacks occurred in series of from two to six every two or three months. Sometimes after a series of major seizures she had a series of "little spells," in which for from a few seconds to a few minutes she became unconscious and the face became bluish, but no tonic or clonic movements occurred. Up to the time when she was first seen, the spells occurred regularly except for a period at the age of 42 when she was without spells for seventeen months while under treatment. Since she was first seen, three years before this paper was written, she had been taking bromides and had had no spells. In 1931, in spite of the fact that this patient had had epilepsy for thirty-one years, and in spite of the fact that she had been treated intensively with bromides for the past three years, she showed not the slightest sign of deterioration or other mental peculiarities, and was efficiently taking care of her home.

CASE 3.—J. A., now aged 24, was first seen on Oct. 25, 1911, at the age of 3 years and 5 months. A second cousin had had "spasms" in infancy, and the mother was "nervous." Birth and the age of walking and talking were normal. At 8 months and again at 16 months, the patient had spasms, each lasting one-half hour, during which he became rigid and unconscious and the eyes rolled back. At the age of 2 years and 9 months, he had an attack starting with a moan, followed by unconsciousness, twitching, rigidity and the passage of urine. The attacks occurred, with few exceptions, every two weeks until he was first seen. At that time he was given bromides which he took religiously for two years. At the time of this report he had had no attacks since he was first seen (i. e., for almost twenty-one years). Since then he had graduated from elementary school, high school and the univer-

sity. While at college he worked every summer, was active in school activities and was manager of the basketball team. Since being out of school he had been active in boy scout work, and was engaged to be married.

Case 4.—Mrs. F. D. was first seen on Oct. 26, 1915, at the age of 14 years. The mother had had migrainous headaches until the age of 40; the family history was otherwise without significance. The patient was born by instrumental delivery and was slightly cyanosed at birth. She walked at 11 months, and at 18 months used sentences. At 7 months she had a convulsion, in which she was unconscious, became rigid and cyanosed, and remained so for a few minutes, following which she was drowsy for a short time. Until she was 4 years of age she had such attacks two or three times a year. Between the ages of 4 and 5 she had several series of convulsions, each series lasting about two hours; she was then free from convulsions for eight years without treatment. At the age of 13 she had an attack characterized by sudden loss of consciousness without cry or aura, and a short tonic and clonic convulsion with biting of the tongue, following which she was drowsy for a few hours. For the next ten months such attacks occurred every two months, and since then (sixteen years) she has had such attacks from one to four times per year. She has never allowed herself to be adequately treated. Without medical direction she has been taking one-half grain (32.4 mg.) of phenobarbital a day for the last sixteen years. When first seen, at the age of 14, she was making normal progress in school. When heard from in 1931, at the age of 30, although having had epileptic spells for twenty-nine years, she was manager of a millinery store. In addition she did her own housework (she had been married in the interim), sang regularly in the church choir and had held office in civic musical organizations.

Case 5.—Miss H. C., now aged 25, was first seen in 1915, at the age of 8½ years. The family history was negative for nervous and mental disorders. The patient was born at full term by a normal labor, walked at 15 months and talked earlier. When 18 months old, she began to have attacks soon after going to bed; she would appear to have a nightmare, would awaken with a slight cry, would be confused and would tremble and shake. She had about six of these attacks in three months and had had none since. At the age of 6, she began to have momentary spells of "dizziness," during which she was confused but apparently not entirely unconscious. At 6½ years, she had a general convulsion in the night lasting from one to two minutes, and awakened with a headache. Eleven months later, she had another general convulsion. These were repeated about every three months until she was seen at the age of 8½. She was then given bromides, which she took regularly for one year; she has never had an attack since (sixteen years). She was graduated from college at the age of 21, and then did two years of graduate work at a university. At the age of 25, although epileptic seizures began almost twenty years before, she was a school teacher in a town of 20,000.

Case 6.—W. P., a physician, aged 68, was last seen on May 8, 1919, at the age of 56. The father died of apoplexy and had been very nervous. The mother had been very nervous. One brother and one sister had epilepsy. At the age of 26, the patient suddenly became unconscious and had a short tonic and clonic convulsion, the entire episode lasting a few minutes. Three years later, while walking along the street, he suddenly became confused, "things didn't look right," and he "felt as though in a dream"; after a few seconds he felt all right. He had no recollection of any similar seizures until the age of 40 (he had taken no medicine in the meantime) when, while sitting at the table, he fell off a chair and was unconscious, but had no convulsion; when he came to, he was confused for a few minutes. Since

then he had had similar seizures from one to four times a year. Since the age of 55, he had had momentary periods of confusion without unconsciousness from one to five times daily. Although for the past twelve years he had taken from 2¼ to 3¾ grains (146 to 242.6 mg.) of phenobarbital daily, the seizures persisted with the frequency stated. In 1931, at the age of 68, although epileptic seizures began forty-two years before, he was still a successful practitioner of medicine and surgery in a town of 15,000.

Case 7.—O. P., a farmer, aged 56, was first seen on June 28, 1915, at the age of 40. A paternal grandmother had been insane; otherwise the family history was negative for nervous and mental disorders. The birth, infantile and developmental history was normal except that when 1 year of age the patient had had a "spasm" under circumstances not remembered. At the age of 7, he began to have attacks during the day or night, which would start with a cry or yell, followed by trembling and accompanied by a feeling of fright and confusion. If the attacks occurred during the day, he would sleep for a few hours afterward. Until the age of 9, the attacks continued regularly; often he would have five in one night. He was then free from attacks until the age of 11, when they recurred at frequent intervals for two years. They then disappeared, returning seven years later, at the age of 20, when they occurred regularly for two years; they returned again at the age of 40, and he had them for two years at frequent intervals, sometimes four or five in twenty-four hours. In the last fourteen years he had had no attacks, but during that time he had taken bromides regularly. Although epileptic seizures began forty-nine years before, and although he had been under treatment with bromides for fourteen years, he had always been able to provide for himself, his wife and six children.

Case 8.—W. G., aged 60, was first seen in 1908, at the age of 37. The family history was negative for nervous and mental disorders. The birth, infantile and developmental history was normal. At the age of 28, he had an attack that began with nodding of the head back and forth; the arms and legs were drawn up for from one to two minutes; he then became unconscious and remained so for ten minutes; during the attack he bit the tongue. Within the next twenty-four hours he had five similar attacks. Three months later he had several similar attacks in one day. He then had similar seizures at intervals of from one week to one month, never more than one per day and not more than three in one week. He continued this way until the age of 37 when he was first seen. He was then given bromides, which he took regularly at first and then irregularly, and was free from seizures for nine years. He then became extremely careless with the medicine, and at the age of 46 he had attacks every two months for a period of one year; these were characterized by unconsciousness, rigidity and biting of the tongue, followed by sleep for a few hours. Since then, that is, for the past four years, he had had no seizures, and had taken bromides irregularly. In 1931, although epileptic seizures started thirty-two years before, and although he had taken bromides regularly for several years, this patient was engaged in the same business that he was in at the time when the attacks started, that of funeral director and furniture dealer in a town of 5,000. He had always been able to support himself and his family.

Case 9.—Mrs. F. F. was last seen in 1919, at the age of 37, and last heard from in 1931, at the age of 49. The family history was without significance except that the mother had been very "nervous" and had had sick headaches. The birth, infantile and developmental history was normal. Since the age of 14, she had been subject to severe attacks of hemicrania, accompanied by blurring of vision and relieved by vomiting or sleep. These came every three months. Since the age of 18 she

had been subject to seizures characterized by an aura of dizziness and indistinct vision, followed by a short period of unconsciousness, with a short tonic spasm and foaming at the mouth. Since the onset these had recurred at intervals of from three weeks to six months. Sometimes she had from four to seven attacks in a series. The patient had taken medicine irregularly. In spite of the fact that this patient had had epilepsy for thirty-one years, she was an efficient housekeeper and took part in community activities.

CASE 10.—Miss I. S. was last seen in 1913, at the age of 21, and last heard from in 1931, at the age of 39. The paternal grandmother and a paternal aunt and uncle had had migraine. The birth, infantile, developmental and school history was normal. When 16 years of age, in the early morning she suddenly fell unconscious and had a generalized clonic spasm. Another similar attack occurred one year later. Three months after this, a like attack occurred, this time with biting of the tongue. In the next four years she had five similar seizures. At this time she was given bromides, which she took fairly regularly for ten years. Since starting medication (eighteen years before this report) she had had no spells with unconsciousness, but had had momentary periods of confusion without unconsciousness from one to four times a year. Although this patient had been an epileptic for twenty-three years, she was a busy teacher of piano, took an active part in musical circles in her town and was chairman of a committee that had for its object the bringing of virtuosi to her city. After her attacks began, she finished a normal course in piano at a first rate conservatory, and from 1926 to 1928 taught piano, went to college and did her own housework.

This study cannot establish the ratio of nondeteriorated to deteriorated patients with epilepsy for the reason that the prevalence of cases showing no deterioration is inadequately treated in the literature. It is not at all unlikely, however, that they far exceed in number the classic deteriorated cases. Many patients, I am sure, are not even seen by neurologists, but wend their way from physician to physician without the real nature of the disorder being determined; a great many never reach physicians' offices, or do so for only a short time, and treat themselves with proprietary remedies.

The question arises as to whether nondeteriorated, extramural patients with epilepsy differ from classic, deteriorated, intramural patients only by the absence of deterioration, or whether they present other differences. Do these two groups differ in hereditary taint, age of onset, sex distribution, frequency of attack, the presence or absence of remissions and the presence or absence of adequate treatment? The following data present an attempt to answer these questions.

HEREDITARY FACTORS

That hereditary factors play an important rôle in the etiology of epilepsy has been recognized by practically all writers. Sieveking[26] found evidences of a neuropathic heredity in 11 per cent of cases,

26. Sieveking, E. H.: On Epilepsy and Epileptiform Seizures, London, John Churchill, 1858.

Reynolds [5] in 31 per cent, Echeverria [7] in 23 per cent, Berger [27] in 32.3 per cent, Moreau [28] in 32 per cent, Binswanger [29] in 36.3 per cent, Dejerine [30] in 66.8 per cent, Hammond [31] in 28 per cent, Aronsohn [32] in 32 per cent, Gowers [8] in 40 per cent, Spratling [9] in 56 per cent, Finckh [33] in 73 per cent, Siebold [34] in 55.2 per cent, Turner [15] in 51 per cent, Oppenheim [35] in from 33 to 50 per cent, Kraepelin [18] in 45.7 per cent, Starr [17] in 35 per cent, Snell [36] in 81.2 per cent and Muskens [23] in 62 per cent.

In the records of 284 nondeteriorated patients the presence or absence of hereditary factors was stated for 266. Of these, 106, or 40 per cent, had an entirely unimportant family history. In the remainder, or 60 per cent, there were evidences of a hereditary neuropathic taint.[37] These figures cannot well be compared with those of most of the writers cited because of the varying conceptions of what constitutes evidence of a neuropathic taint. Some considered only epilepsy, and others only epilepsy and insanity, and some included rheumatism, alcoholism, etc.

The writer whose data best lend themselves for comparison with mine is Snell. In 345 cases he found evidences of a neuropathic taint in 81.2 per cent—a ratio 21.2 per cent higher than a study of the present series discloses. From this it seems reasonable to believe that hereditary neuropathic taint is more frequent in institutional epileptic patients than in nondeteriorated patients of the outside world.

A further comparison of Snell's data regarding heredity with those of the present series disclosed some interesting differences. In my series a neuropathic factor could be detected in the direct line (parents) in 44 per cent, in the indirect line (grandparents, uncles and aunts) in 11 per cent and in siblings only in 5 per cent. In table 2 I have compared these data with similar data for institutional cases. This table shows

27. Berger, O., quoted by Binswanger (footnote 29).

28. Moreau, quoted by Binswanger (footnote 29).

29. Binswanger, O.: Die Epilepsie, Vienna, Alfred Hölder, 1899.

30. Dejerine, quoted by Turner (footnote 15).

31. Hammond, W. A.: A Treatise on the Diseases of the Nervous System, New York, D. Appleton and Company, 1890.

32. Aronsohn, O.: Heredität bei Epilepsie, Neurol. Centralbl. **13**:631, 1894.

33. Finckh, J.: Beiträge zur Lehre von Epilepsie, Arch. f. Psychiat. **39**:820, 1904-1905.

34. Siebold: Statistische Beiträge zur Aetiologie der Epilepsie, Psychiat.-neurol. Wchnschr. **8**:1147, 1906.

35. Oppenheim, H.: Text-Book of Nervous Disease, translated by A. Bruce, Chicago, Chicago Medical Book Company, 1911.

36. Snell, O.: Belastungsverhältnisse bei der genuinen Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **70**:1, 1921.

37. That is, evidences in the family of functional psychosis, psychoneurosis, nervousness, migraine, epilepsy, alcoholism, senile psychosis, psychopathic personality, suicide or feeblemindedness.

that the nondeteriorated patients show a smaller percentage of hereditary taint in all three lines, especially in the direct and indirect.

In the direct line (parents) Snell found psychosis in 5.96 per cent, nervous disorders in 17.15 per cent, of which 4.9 per cent were epilepsy, alcoholism in 24.15 per cent, apoplexy [38] in 5.39 per cent, senile dementia in 0.28 per cent, psychopathic personality in 10.79 per cent and suicide in 0.85 per cent. How these data compare with those obtained in the present series of nondeteriorated patients is shown in table 3. Migraine and nervousness were more common in the parents of the nondeteriorated patients, but psychosis was eight and a half times as frequent in

TABLE 2.—*Percentage of Cases of Epilepsy in Institutional Patients and in the Present Series of Nondeteriorated Patients, in Which a Neuropathy Occurs in the Direct Line (Parents), Indirect Line (Grandparents, Uncles and Aunts), and Siblings Only*

	Institutional	Extramural (This Series)
Direct	59.09	44
Indirect	16.77	11
Siblings only	5.4	5
Total	81.26	60

TABLE 3.—*Percentage of Cases of Epilepsy in Institutional Patients and in the Present Group of Nondeteriorated Patients, in Which the Various Neuropathic Taints Occurred in the Direct Line (Parents)*

	Psychosis	Nervous Disorders	Alcoholism	Apoplexy	Senility	Psychopathic Personality	Suicide
Institutional patients (Snell)	5.96	17.15*	24.15	5.39	0.28	10.79	0.85
Present series	0.7	37.9 †	3.0	2.2	0	0	0

* Epilepsy occurred in 4.94 per cent.
† Migraine was noted in 24.4 per cent, epilepsy in 1.5 per cent and nervousness in 12 per cent.

the institutional patients as in the extramural ones; epilepsy, three times as frequent; alcoholism eight times as frequent; apoplexy, more than two and a half times as frequent. In the present series no patients were found whose parents had senile dementia or psychopathic personality or had committed suicide, while in Snell's institutional patients psychopathic personality in the parents was quite common and senile dementia and suicide, while not so common, were not rare. It thus appears that the parents in the more malignant, deteriorated institutional cases of epilepsy are much more heavily burdened with neuropathy than are the parents of the sane extramural epileptic patients.

A study of the entire families in the present series also disclosed some significant differences from data obtained from similar studies

38. Strictly speaking, not a nervous but a vascular disorder.

by Snell. In my series, the 266 nondeteriorated patients had 316 relatives showing evidences of a neuropathic taint. These were distributed as follows: psychosis, 7; migraine, 133; nervousness, 112; epilepsy, 31; alcoholism, 13; apoplexy, 12; psychopathic personality, 3; suicide, 3, and feeblemindedness, 2.

Expressed in terms of percentage, it was found that of the 316 neuropathically tainted relatives, 2.0 per cent had a psychosis, 42.1 per

TABLE 4.—*Distribution of Neuropathy Among the Relatives of Institutional Patients and the Present Series of Nondeteriorated Patients With Epilepsy*

	Psychosis, per Cent	Nervous Disorders, per Cent	Alcoholism, per Cent	Apoplexy, per Cent	Senile Dementia, per Cent	Psychopathic Personality, per Cent	Suicide, per Cent
Institutional patients (Snell): 502 factors in 345 cases	22.51	28.28*	25.89	6.57	0.59	13.34	2.79
Present series: 316 factors in 266 cases	2.0	87.9 †	4.1	3.7	0	0.9	0.9

* Epilepsy in 11.75 per cent.
† Migraine in 42.1 per cent; nervousness in 35.4 per cent; epilepsy in 9.8 per cent, and feeblemindedness in 0.6 per cent.

TABLE 5.—*The Percentage Frequency of Epilepsy, Insanity and Alcoholism as Hereditary Factors in Patients with Epilepsy as Mentioned by Some Authors and Noted in This Series of Nondeteriorated Epileptic Patients*

Authors	Epilepsy	Insanity	Alcoholism
Sieveking [26]	11.1	....	....
Echeverria [7]	10.4	....	....
Dejerine [30]	21.2	16.8	51.6
Féré (Les épilepsies et les épileptiques, Paris, Félix Alcan, 1890)	....	....	38.3
Starr [17] *	7.0	....	9.3
Hammond [31]	16.1	12.1	....
Aronsohn [32]	18.0	....	....
Voisin (quoted by Turner [15])	....	....	31.0
Binswanger [29]	11.0	29.6	22.0
Gowers [9]	30.3	13.6	....
Doran (Am. J. Insan. **60**: 61, 1903)	19.3	7.9	21.6
Spratling [9]	16.0	7.0	14.0
Finckh [33]	24.2	15.9	18.9
Turner [15]	37.2	5.4	3.1
Kraepelin [18]	14.3	....	....
Muskens [23]	35.7	14.5	8.9
This series	7.5	3.0	4.5

* Cases from private practice and outpatient clinic.

cent had migraine, 35.4 per cent had nervousness, 9.8 per cent had epilepsy, 4.1 per cent were alcoholic, 3.7 per cent had had apoplexy, 0.9 per cent had psychopathic personalities, 0.9 per cent were suicides and 0.6 per cent were feebleminded. A comparison of these data with similar data obtained from a study of 502 relatives of Snell's institution patients showed some interesting differences. The relatives of extramural patients had more migraine and nervousness, but in the relatives of the institution patients psychosis was more than eleven times as

common as in the relatives of the patients in the present series; alcoholism was six and a half times as frequent, and apoplexy, psychopathic personality and suicide twice, thirteen times and three times as common, respectively, as in the relatives of the sane patients with epilepsy. The relatives of institution patients had 1.85 per cent more cases of epilepsy among them than did those of the extramural patients. From this it seems that not only the parents, but all relatives of institution patients carry a heavier load of neuropathy than do those of the epileptic persons who adjust in the outside world.

Most other writers on the heredity of persons with epilepsy have looked for the presence of epilepsy, insanity and alcoholism mainly in the families of their patients. Some paid attention to all three conditions, and others to but one or two. In the present series of non-deteriorated patients epilepsy was found in the family history in 7.5 per

TABLE 6.—*Percentage Occurrence of Age of Onset of Epilepsy as Given by Some Authors and as Noted in the Present Series*

	To 5 Yrs.	6-10 Yrs.	11-15 Yrs.	16-20 Yrs.	21-25 Yrs.	26-30 Yrs.	31-40 Yrs.	41-50 Yrs.	51-60 Yrs.	61-70 Yrs.	71-80 Yrs.	Cases Occurring after 25 Yrs.
Spratling	26.2	19.2	24.5	13.7	5.4	3.3	4.0	1.0	0.6	1.8	....	10.6
Turner	17.0	14.3	28.1	18.6	6.9	5.3	5.8	2.6	1.0	0.4	....	15.1
Starr	18.1	13.3	20.1	17.8	12.3	6.6	8.4	3.1	0.9	0.3	....	19.3
Ricci	14.0	17.8	15.5	12.7	7.1	5.1	1.8	1.0	0.5	0.8	....	9.2
Siebold	32.8	13.4	22.7	14.1	6.0	3.2	2.9	1.6	9.5	0.3	0.1	17.6
Kraepelin	12.4	10.9	18.9	20.4	12.6	12.1	8.3	2.8	0.8	0.8	0.1	24.9
Present series	11.6	13.3	18.3	15.5	9.8	12.3	11.2	7.3	0.7	...	...	31.5

cent, insanity in 3.0 per cent and alcoholism in 4.5 per cent. How these figures compare with similar data of other writers is shown in table 5. A study of this table shows that figures for these values as given in the literature far exceed those obtained in the present study, with only one exception. Starr found that in his patients there was a history of epilepsy in the family in 7 per cent, or 0.5 per cent less than I found, but he studied patients outside an institution; his patients were in private practice or in outpatient clinics. This table affords further evidence of the differences in heredity between patients institutionalized because of mental changes and those who are well adjusted outside of an institution.

AGE OF ONSET

Table 6 shows the percentage distribution of the age of onset through the various age periods in the series of Spratling,[9] Turner,[15] Starr,[17] Ricci,[39] Siebold [34] and Kraepelin [18] and the present one. A study of this table shows that in the present series fewer patients showed the

39. Ricci, quoted by Kraepelin (footnote 18).

onset before the age of 5 (11.6 per cent) than in any of the other series, although this figure was closely approximated in Kraepelin's cases (12.4 per cent); in the other series this value is appreciably higher, reaching its maximum in Siebold's cases (32.8 per cent). In the present series 31.5 per cent of the cases showed the onset after the age of 25; this is considerably greater than the same value in any of the other series (Spratling, 10.6 per cent; Turner, 15.1 per cent; Starr, 19.3 per cent; Ricci, 9.2 per cent; Siebold, 17.6 per cent, and Kraepelin, 24.9 per cent).

It thus appears that in nondeteriorated extramural epileptic patients there is a tendency toward a later onset than in deteriorated incarcerated patients.

SEX DISTRIBUTION

Echeverria,[7] Delasiauve [6] and Gowers [8] reported a preponderance of females with epilepsy. Osler,[40] Hammond,[31] Spratling,[9] Starr,[17] Reynolds,[5] Finckh [33] and Kraepelin [18] reported a preponderance of males.

TABLE 7.—*Sex Distribution of Patients with Epilepsy as Given by Some Authors and in This Series*

	Males, per Cent	Females, per Cent
Delasiauve	33.3	66.6
Reynolds	55.5	44.5
Echeverria	42.1	57.9
Hammond	52.8	47.2
Gowers	48	52
Finckh	56	44
Spratling	55.5	44.5
Starr	58.1	41.9
Osler	53.3	46.7
Kraepelin	73	27
Present series	61.9	38.1

In the present series of nondeteriorated patients males exceed females in the ratio of 61.9 to 38.1. Table 7 shows how this compares with the sex distribution as given by other writers. There is a greater preponderance of males in my series than in any other series except that of Kraepelin, who found the ratio to be 73 to 27. This may be of some significance. It may possibly lend evidence to support a view that males are less liable to deterioration. However, in view of the outstanding exception and of the different opinions regarding sex distribution, attempts to correlate deterioration with sex must be considered futile at present.

FREQUENCY OF ATTACKS AND REMISSIONS

In table 8 I have compared the frequency of major seizures in the institutional patients of Gowers,[8] Spratling [9] and Turner [15] with the

40. Osler, W.: The Principles and Practice of Medicine, revised by T. McCrae. New York, D. Appleton and Company, 1930.

frequency in the present series. In the latter the frequency could be determined in 238 cases. A study of this table shows that the major seizures are much more frequent in institutional patients. Thus, in Gowers' patients 11 per cent had major seizures at intervals not exceeding one day; in the present series, only 0.8 per cent. In Gowers' patients intervals not exceeding one week occurred in 38 per cent; in Spratling's, in 56 per cent; in Turner's, in 42.3 per cent, and in the present series in only 8.7 per cent. Intervals of over four months occurred in 5 per cent of Gowers' patients, in 2.25 per cent of Spratling's, in 6.0 per cent of Turner's and in 17.5 per cent of the present series.

TABLE 8.—*Percentage Frequency of Major Attacks as Given by Gowers, Turner, Spratling and as Noted in This Series*

	Gowers	Spratling	Turner	Present Series
Interval not exceeding 1 day	11	56.0	12.0	0.8
More than 1 day, not more than 1 week	27		30.3	7.9
More than 1 week, not exceeding 2 weeks	15	12.3	30.3	12.7
More than 2 weeks, not exceeding 1 month	24	22.0		25.2
More than 1 month, not exceeding 2 months	10	6.5	20.5	11.7
More than 2 months, not exceeding 4 months	8			23.9
More than 4 months, not exceeding 6 months	2	2.2	6.0	6.7
More than 6 months, not exceeding 12 months	2			3.7
Over 12 months	1			7.1

In a thorough search of the literature I could find only one statistical statement regarding the frequency of petit mal attacks; Gowers [8] stated that in half the cases the attacks occur daily. In my series the frequency of petit mal seizures could be determined in 131 cases. They occurred at intervals not exceeding one day in 21.3 per cent, a figure less than half of that of Gowers. In the remainder of the present series they occurred as follows:

Intervals of more than one day, not exceeding one week, in 22 per cent.
Intervals of more than one week, not exceeding two weeks, in 18.3 per cent.
Intervals of more than two weeks, not exceeding one month, in 18.3 per cent.
Intervals of more than one month, not exceeding two months, in 6.0 per cent.
Intervals of more than two months, not exceeding four months, in 6.7 per cent.
Intervals of more than four months, not exceeding six months, in 2.2 per cent.
Intervals of more than six months, not exceeding twelve months, in 1.5 per cent.
Intervals of more than twelve months, in 3.8 per cent.

An extensive study of remissions in institutional cases of epilepsy was made by Turner.[15] In 1,000 cases he found that there were 44 remissions of over two years, some with and some without treatment.

He found a remission of two years in 5 instances, of three years in 16, of four years in 7, of five years in 4, of six years in 1, of seven years in 2, of eight years in 1, of nine years in 1, of ten years in 1, of twelve years in 1, of thirteen years in 1, of fifteen years in 1, of nineteen years in 1 and of thirty years in 1. In the present series of extramural patients remissions were much more frequent. Of the 284 patients, 86 had had 104 remissions of over two years, of which 63 occurred during or after adequate treatment and 41 with none or with inadequate treatment. Neither Turner's data nor mine include as remissions the oftentimes long intervals between the first and second, and second and third attacks. In the present series there were 34 remissions of two years; 14 of three years; 10 of four years; 8 of five years; 6 of six years; 3 of seven years; 4 of eight years; 2 of nine years; 3 of ten years; 12 of from eleven to fifteen years, and 8 of from sixteen to twenty-one years.

The comparison regarding the frequency of seizures and the frequency and duration of remissions shows that institutional patients have both grand and petit mal seizures more frequently than do the nondeteriorated extramural patients, and that in the latter remissions last longer.

SUMMARY AND CONCLUSIONS

Almost all the descriptions of epilepsy have been written by physicians in institutions on studies of institutional patients. Since epileptic patients are sent to institutions largely because mental changes develop, these writers state that mental changes occur in an overwhelming percentage of epileptic patients; some say that all persons with epilepsy deteriorate. These writers, however, did not know of the existence of a large number of persons with epilepsy who adjust and succeed outside an institution and who do not deteriorate. A study of 304 patients in private practice who had had epilepsy for over six years, and in some instances for two, three or four decades, revealed that only 20, or 6.5 per cent, had become deteriorated; the rest carried on in the world the same as their fellow men. A further study of the nondeteriorated patients showed that they differed in several respects from the deteriorated ones. They came of a stock less heavily burdened with neuropathy; the onset in the nondeteriorated patients was on the whole somewhat later; they had attacks less frequently, and they had more and longer remissions.[41]

41. Since this article was written there has appeared a paper by William G. Lennox and Stanley Cobb (The Non-Institutional Epileptic, Epilepsy and the Convulsive State, Association for Research in Nervous and Mental Disease, Baltimore, Williams & Wilkins Company, 1931, vol. 7). Owing to the nature and brevity of the paper, the data given in it do not lend themselves to comparison with mine. I should like also to call attention to Dr. Collier's discussion which emphasizes the importance of studying extramural cases of epilepsy.

THE THYROID FACTOR IN FAMILY PERIODIC PARALYSIS

REPORT OF A CASE

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Toward the end of the nineteenth century, much interest was manifested in the study of a pathologic syndrome termed family periodic paralysis. Admirable reviews of the "disease" were written by Singer and Goodbody [1] and by Taylor.[2] Other notable contributions were made by Goldflam,[3] Oppenheim,[4] Mitchell,[5] Westphal [6] and others. It was not, however, until the ingenious experiments of Shinosaki [7] that any recent notable advances were made. In his summary paper of 1926, the relationship of family periodic paralysis to disturbances in the functions of the glands of internal secretion is stressed on the basis of numerous experiments. Heretofore, many other factors were considered in an attempt to elucidate the pathogenesis of periodic paralysis. Such theories, which considered malaria, scarlet fever, auto-intoxication, heredity, physical overexertion, indiscretions in diet, emotions and even internal secretory disturbances as important etiologic factors, were never

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From the Gastro-Enterological and Neurological Clinics of the Department of Medicine, University of Maryland.

1. Singer, H. D., and Goodbody, F. W.: A Case of Family Periodic Paralysis, With a Critical Digest of the Literature, Brain **24**:257, 1901.

2. Taylor, E. W.: Family Periodic Paralysis, With a Report of Cases Hitherto Unpublished, J. Nerv. & Ment. Dis. **25**:637, 1898.

3. Goldflam, S.: Ueber eine eigentümliche Form von periodischer familiäre, wahrscheinlich auto-intoxicatorischer Paralyse, Wien. med. Presse **31**:1418, 1890; Ztschr. f. klin. Med. (supp. vol.) **19**:240, 1891.

4. Oppenheim: Neue Mitteilungen über den von Prof. Westphal beschriebenen Fall von periodischer Lähmung aller vier Extremitäten, Charité Ann. **16**:350, 1891.

5. Mitchell, J. K.: A Study of a Case of Family Periodic Paralysis, Am. J. M. Sc. **118**:513 (July-Dec.) 1899.

6. Westphal, C.: Ueber einen merkwürdigen Fall von periodischer Lähmung aller vier Extremitäten, mit gleichzeitigem Erlöschen der elektrischen Erregbarkeit während der Lähmung, Berl. klin. Wchnschr. **32**:489, 1885.

7. Shinosaki, T.: Klinische Stüdien über die periodische Extremitätenlähmung, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:564, 1926.

adequately supported by substantial and conclusive data. In his work, Shinosaki experimented with extracts of glands of internal secretion, with hypofunctioning and hyperfunctioning endocrine glands and with various diets as well. As a result of a most thorough study he concluded that family periodic paralysis was the outcome of a polyglandular dysfunction.

Recently, Dunlap and Kepler [8] reported four cases in which the occurrence of periodic paralysis seemed to depend on the existence of a state of hyperthyroidism. In these cases the association was so intimate and unmistakable that alleviation of the state of hyperthyroidism was followed by disappearance of the recurring paralytic attacks. They believed that at least two possible explanations present themselves: either (1) "that the patient may have a latent tendency to the development of periodic paralysis, in which instance the exophthalmic goitre may act merely as an inciting factor in the precipitation of the disease," or (2), more plausibly, "that there may be some physiologic or chemical change occurring in the muscles in cases of exophthalmic goitre, which is not understood, and which is directly responsible for the production of transient paralysis in these cases." In a complete review of the literature dealing with family periodic paralysis, these authors [9] found only a few articles that spoke of its association with goiter.

All these ideas, and especially that of polyglandular disturbance, are interesting, and although at the present stage of knowledge no definite conclusions may be reached, the possibility that an etiologic understanding may be disclosed is at least encouraging.

We have had the good fortune to follow a case of family periodic paralysis associated with exophthalmic goiter over a period of more than three years, including a long postoperative interval. The findings before and after operation are of more than passing interest, important in throwing some light on the relationship of family periodic paralysis not only to exophthalmic goiter but to other glands of internal secretion as well.

REPORT OF CASE

History.—A man, aged 24, was seen in the clinic of Dr. Julius Friedenwald on April 28, 1928. At that time he complained of "nervousness," irritability, constipation and attacks of "paralysis" of the extremities. The family history was essentially unimportant. There was no history of family periodic paralysis. His past history was unimportant, except for an attack of influenza in 1918. He had been

8. Dunlap, H. F., and Kepler, E. J.: Occurrence of Periodic Paralysis in the Course of Exophthalmic Goitre, Proc. Staff Meet., Mayo Clin. **6**:272 (May 6) 1931.

9. Dunlap, H. F., and Kepler, E. J.: Personal communication.

wearing glasses since November, 1924, and this time was placed as the probable beginning of his present thyroid condition. He said that he had not had venereal infection. His habits were normal.

The present condition is believed to have had its onset about September, 1927, when he was awakened at night by a peculiar paresthetic phenomenon over the lower extremities and stiffness in the musculature, especially in the lower extremities. On attempting to arise, he found that he could not move. This condition lasted for three hours and then cleared up as rapidly as it had commenced. Following the attack, the patient felt tremulous and weak and for a short period was markedly unstable on his feet, but he suffered no physical pain.

Several days later, he resumed employment and carried on without interruption until about a month later, when a similar attack occurred. He attributed the attacks to certain dietary indiscretions. Since that time he had had approximately fifteen or twenty attacks at varying intervals of from two in one week to as long as several months apart. The duration of the attacks was from several hours to a maximum of forty hours, the latter period of involvement occurring just prior to admission to the hospital. This attack occurred two days before admission, beginning just after the patient had retired. On the next day he could move neither his legs nor his arms. He felt extremely weak and had to remain in bed. In that condition he was taken to the hospital. There was no pain or sensory disturbance at any time. He had, however, often felt that evacuation of the bowels following a dose of magnesium sulphate strengthened him when he thought an attack was coming on and often seemed to avert the attack. During the attacks the patient was always markedly constipated and suffered unusual thirst, his lips being dry and parched.

Physical Examination.—The patient was an undernourished male adult, who lay quietly in bed. The cranium and scalp were normal. The skin and mucous membranes were of good color. There were moderate exophthalmos and moderate widening of the palpebral fissures, with positive von Graefe-Stellwag and Moebius signs. There was slight weakness of the right internal rectus, which was considered to be of muscular origin. No edema of the lips was noted. The pupils were central, circular and regular in outline and reacted promptly to light and in accommodation. The visual fields and the sympathetic ocular reflexes were normal. Vision was good, and the fundi were normal. There were no facial asymmetries. There was no involvement of the cranial nerves. He had several carious teeth; the gums were in fair condition. The tongue was normal and protruded in the midline. The tonsils were hypertrophic, especially the left. The pharynx was hyperemic. The nose and ears were normal. A moderate enlargement of the thyroid, both of the isthmus and of the lateral lobes, was present. There was no thrill or bruit. The lungs and heart were normal. The motor system showed moderate hypotonicity of the entire skeletal musculature. There was some general emaciation, but no atrophy or fibrillations. There was an intention tremor of the thyroid type, involving the hands. Speech was normal. There was no weakness of the sphincters. The grip of the right hand was 70, and that of the left 54. No kinesthetic disturbances were noted. The patient executed the finger-to-finger and heel-on-tibial crest tests without difficulty. Station and gait were normal. There seemed to be some vague paresthetic phenomenon associated with the attacks, but sensory examination gave normal results. The reflexes were equal and slightly accentuated, both superficial and deep. There was no clonus, and the plantar response was normal. The pulse vacillated between 100 and 140. The blood pressure was 130 systolic and 30 diastolic.

Course.—On May 3, a basal metabolic test showed a rate of plus 50 per cent. Compound solution of iodine was administered, and on May 15 the metabolic rate was reduced to plus 25 per cent. On May 26, it had risen to 35 per cent. In the meantime, the temperature had been normal, the pulse rate averaging about 100.

An Attack.—On May 11, at 9:30 p. m., the patient experienced a peculiar weakness of the lower extremities while returning from the bathroom. He reached the bed, and after lying down became "nervous" and could not sleep. At 11 p. m., he was unable to raise any of the four extremities. Examination at this time revealed that the cranial nerves were essentially normal. No fibrillations were detected. The skeletal musculature was markedly hypotonic throughout, there being a flaccid paralysis of all four extremities. There was no weakness of the sphincters. Speech was not affected. The reflexes, both superficial and deep, were lost. This attack lasted for about six hours. Following the attack, the patient felt very unstable and restless, and expressed some insecurity in standing or walking. However, no kinesthetic disturbances were elicited. No sensory abnormalities were noted. At this time, the reflexes were equal and somewhat hyperactive, as had been noted in the first examination.

Operation and Course.—On May 30, a thyroidectomy was performed, ethylene anesthesia being used. The patient's condition was good, and the postoperative recovery was uneventful. Microscopic examination of the gland revealed a condition essentially typical of exophthalmic goiter.

On May 20, the metabolic rate was plus 29 per cent, and on June 10 it remained unchanged. The patient began to gain weight, became less nervous and slept well. The pulse rate fell to 80 and averaged about 90 per minute. Except for a slight postoperative rise in temperature, the patient did well. Other examinations of the urine, stools, phthalein kidney function, the Wassermann reaction of the blood and the blood count were always normal. The patient was discharged on June 13, 1928, having been in the hospital forty-five days. Improvement was marked.

Since discharge from the hospital, the patient has been seen at frequent intervals. On July 7, he had an abortive attack of weakness during which he could walk, though with some difficulty, and which lasted only a few minutes and then disappeared. On August 29, he was found to be very well; the blood pressure was 100 systolic and 70 diastolic, and he had gained some weight. A neurologic examination disclosed no abnormal conditions. There had been no attacks.

On Dec. 8, 1928, he was seen again. He had had no attacks, had continued to gain in weight and felt very well "except for being a little nervous." A long interval followed, and he was not seen again until Oct. 1, 1929, when he was found to have diseased tonsils. During that entire interval he had had only one very mild attack of weakness without paralysis. He exhibited, at this time, signs of recurrent thyroid hyperactivity, and it was thought that the tonsillar infection might be responsible. Accordingly, the tonsils were removed on October 9. He then was well until November 18, when he reported a mild attack of paralysis of short duration. On December 14, he reported another attack of weakness. On December 22, he was again well; on December 24, the basal metabolic rate was reported as minus 10 per cent. When he was again seen on April 2, 1930, he was well, but was still experiencing noticeable attacks of weakness, particularly at night after going to bed. At this time, however, a neurologic examination gave normal results. On April 22, he reported three attacks of weakness of the legs and arms, of short duration, more marked, he thought, on the right side. From April 22, 1930, until July, 1931, the patient communicated with us and reported that he was getting along very well.

In July, 1931, when he was last seen, he was found to be in excellent physical condition. The muscular tone, the reflexes and, in fact, the entire neurologic system were normal. He had gained more weight than he desired, but other than this he was doing splendidly, being well able to carry on night work in a postoffice. He was not aware of easy fatigability and had had no difficulty in walking. On the other hand, he is reminded about every six months of the old paralytic condition, for at these times he is aware of more or less weakness in the extremities. Between April 22, 1930, and July 19, 1931, he had had only one attack of paralysis of all four extremities. This lasted for three or four hours and occurred after a night of strenuous work. The attack came on after "working hours," when he was preparing to go to bed. The patient had noticed that since the operation the attacks usually occurred after work or while in bed, whereas before they appeared at any time, frequently during working hours. Concerning treatment, little in addition to general healthful measures has been advised. The diet has been essentially normal, except for a slight decrease in carbohydrates. He has taken no medication.

DIAGNOSIS AND COMMENT

Clearly the case presented is one of marked hyperthyroidism associated with attacks of periodic paralysis. Very little is known regarding the etiology of the associated condition. Auto-intoxication has been suggested by many investigators, and extensive researches into metabolism have been made.[10] Other theories regarding pathogenesis and etiology have been exploited, invariably, however, with little convincing supporting evidence. Examinations of bodily secretions and excretions have been made, always with the object of finding the evasive toxin. Changes in bodily functions and in physical signs before, during and after an attack were offered as evidence in favor of the auto-intoxication theory. These changes are not constant, and whereas in one case the heart may show signs of temporary dilatation with irregularity in beat and the presence of a mitral systolic murmur, another case may show only albumin in the urine and still another may show no changes whatever.

The important fact brought out by the present case is that hyperthyroidism and periodic paralysis may be intimately associated. This idea is not new, since Shinosaki and others have already written of it. However, the remarkable point in this case is the subsequent history. Thyroidectomy was performed, but the attacks continued. Yet the attacks have been definitely less marked, since they occur not only less frequently but with diminished intensity. They have been transformed from attacks of paralysis to, for the most part, spells of weakness.

Shinosaki was very emphatic in his belief that periodic paralysis is a polyglandular disease, and of the glands associated with it he mentions the thyroid as the most prominent. In his opinion the so-called

10. Osler: Principles and Practice of Medicine, ed. 10, New York, D. Appleton & Company, 1927, p. 961.

basedowian paraplegia of Charcot is nothing other than periodic paralysis combined with exophthalmic goiter. We take the liberty of quoting from Barker's work on metabolism, in which Howard [11] discussed the muscular weakness noted in hyperthyroidism. He stated in part:

> Charcot has noted a rare sign in paraparesis of the sudden giving away of the legs like that seen in intermittent claudication. It was noted by Mackenzie in twelve cases, and considered by him as functional in origin though without other symptoms of hysteria. On the other hand, weakness of the legs in climbing stairs, or even in walking, is quite frequent. . . . The myasthenia may be cerebral in origin, or possibly like myasthenia gravis be associated with the thymus hyperplasia, which is so common in Graves' Disease.

Although there is some resemblance between basedowian paraplegia and periodic paralysis, the conditions are not exactly alike, and one is therefore not justified in accepting them as one and the same without more convincing evidence.

In our case the improvement was indisputable, but there was no cure. This may be explained by assuming that the operation was not successful, that is, that a mild hyperthyroidism continued to exist, and that its existence explained the attacks of weakness and paralysis. Since the basal metabolic rate remained high for some time following the operation, since tachycardia and "nervousness" were undoubtedly present more often than usual, and since the exophthalmos persisted, this assumption is not altogether improbable. On the other hand, it may be concluded that there is no relationship between the two diseases, and that their presence in the same patient is merely coincidental. But this does not explain the reports of other investigators in whose cases cure of the hyperthyroid condition eradicated the attacks of periodic paralysis. It is possible also that the presence of hyperthyroidism has only a modifying tendency, and that its cure favorably affects the periodic paralytic syndrome, since it allows the body to focus its energy and resistance on the latter disease. When thyroidectomy cures a patient of hyperthyroidism as well as of period paralysis, we might assume that the glandular dysfunction was just enough to upset the general bodily metabolism and allow for the imbalance (in toxin excretion or what not) which may cause periodic paralysis.

If periodic paralysis is a polyglandular disease, and that seems probable in the present state of knowledge, why is it that many cases show no glandular dysfunction whatever? Is it simply that one cannot discover the latter, or must one conclude that other mechanisms are involved? If the disease is associated with thyroid imbalance, we are unable to explain the cases in which the thyroid glands are apparently

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11. Howard, C. P.: Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, vol. 1, p. 349.

normal. Not all of Shinosaki's cases were associated with thyroid disturbances; other causes, such as disturbed carbohydrate metabolism, were prominent. However, fourteen of twenty-four cases showed struma, and of these, six were cases of exophthalmic goiter. Moreover, paralytic attacks could be induced in some of these patients by the administration of thyroid preparations. In three cases of struma glycosuria was present, and in 73 per cent of the cases albuminuria was found, again suggesting a metabolic imbalance.

These data support the idea of a polyglandular disease. In addition, Shinosaki found that injection of epinephrine in fifteen cases caused paralytic attacks in two, while in one case ventricular extrasystoles occurred as they had done previously in a spontaneous attack. The results of carbohydrate variation, the blood sugar observations and the effect of parathyroid preparations all give evidence, not by any means conclusive, that favors a theory of polyglandular disease rather than other theories, such as Schmidt's attempt to bring the disease in relation to a local ischemia of small arteries in muscle, or Lundborg's theory that the disease is due to hyperfunction of the parathyroid glands alone.

In the four cases of Dunlap and Kepler, the occurrence of paralysis seemed dependent on the presence of hyperthyroidism. In their series of seven cases there were no differences in the signs and symptoms in the cases with or without hyperthyroidism so far as the periodic paralytic attacks were concerned, except that the attacks occurred later in life when disease of the thyroid gland was present. It is remarkable that all four patients having an associated thyroid disease were cured of periodic paralysis following treatment for the thyroid condition. Such results almost preclude the possibility of a hysterical basis for the paralytic attacks. In our case the result was not so decisive, although it, too, points to an endocrine etiologic factor.

SUMMARY AND CONCLUSION

We have presented a case in which exophthalmic goiter and periodic attacks of paralysis coexisted. It was learned that treatment for the diseased thyroid resulted in partial alleviation of the paralytic attacks. This result is significant in view of the actual cures in four cases of periodic paralysis that were reported by Dunlap and Kepler in which thyroid disease was also present. These observations suggest the possibility of an endocrine factor in the causation of periodic paralysis. Such a hypothesis has been advanced by Shinosaki and supported more or less by his experimental researches. We do not believe that thyroid disease in itself is the etiologic agent in periodic paralysis, but we suggest, as does Shinosaki, that the latter disease appears as the result

of a polyglandular disturbance. It may be that periodic paralysis, or more correctly, family periodic paralysis, is not an entity. There may be several types with different etiology, all characterized, when typical, by heredity, periodicity, confinement to the motor portion of the nervous system, electrical changes and practically perfect health of the patient in the free intervals. It does seem, however, that in a certain group of cases the endocrine element plays an indisputable rôle which is doubtless of etiologic importance. It offers, therefore, a method of more or less hopeful treatment for a disease which heretofore was allowed, unchecked, to run its chronic course. Rest, diet and the usual symptomatic measures may, we believe, be aided immeasurably in certain cases by iodine therapy, subtotal thyroidectomy and other therapeutic endocrine procedures. Admittedly, the last word has not been said; only a hopeful idea has been evolved; there remains the need of further observation and research before its full value is known and appreciated.

FAMILIAL PROGRESSIVE BULBAR PARALYSIS

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Progressive bulbar paralysis [1] is an uncommon disease occurring usually in the fifth and sixth decades of life, rarely before the age of 30. It begins insidiously and progresses slowly. The muscles of the lips, tongue, pharynx, larynx and jaws, at first only weakened, later become paralyzed and atrophied, which produces difficulties of speech, deglutition, phonation and mastication. The disease process is a degenerative one causing gradual destruction and finally complete atrophy of the nerve cells forming the most important components of the motor portion of the lower cranial nerves.

Although much has been learned about the etiologic factors involved in the acute forms of bulbar paralysis,[2] anterior poliomyelitis and associated diseases, the cause of true progressive bulbar palsy is just as obscure today as when the condition was first recognized by Duménil [3] in 1859. The gamut of possible factors has been run in an effort to determine the causative agent, and one reads that exposure to cold, trauma, overuse or exhaustion of the muscles of the mouth and tongue (e. g., by glass-blowers, players of wind instruments, etc.), toxemias (e. g., lead intoxication, diphtheritic poisoning), syphilis, Bright's disease, emotion and influenza [4] have been held responsible. Further, the condition has been said to occur in association with or as a part

From the Neurological Service of the University Hospital.

1. Wachsmuth: Ueber progressive Bulbärparalyse und Diplegia facialis, Dorpat, 1864. Duchenne: Paralysie musculaire progressive de la langue, du voile du palais et des lèvres, maladie non encore décrite, Arch. gén. de méd. **2**:283 and 431, 1860. Trousseau, A.: Paralysis glosso-laryngea, Med. Klin. d'Hôtel-Dieu, Paris, 1861. Leyden, E.: Vorläufige Mitteilung über progressive Bulbärparalyse, Arch. f. Psychiat. **2**:423, 1870; Ueber progressive Bulbärparalyse, ibid. **2**:643, 1870. Kussmaul, A.: Ueber die fortschreitende Bulbärparalyse und ihr Verhältnis zur progressiven Muskelatrophie, Samml. klin. Vortr. no. 54, 1873, p. 439 (Inn. Med. no. 20).

2. Gerlach, F., and Kress, F.: Ueber Granulabefunde im Zentral-Nervensystem bei Pseudolyssa (Paralysis bulbaris infectiosa Aujeszky) und experimenteller Poliomyelitis anterior acuta, Arch. f. wissensch. u. prakt. Tierh. **63**:53 (March 16) 1931.

3. Duménil: Atrophie des nerfs hypoglosses, faciaux et spinaux; paralysie complète du movement dans la langue incomplète à la face, Gaz. hebd. de méd. **6**: 390, 1859.

4. Ellison, W. A.: Progressive Bulbar Palsy, U. S. Vet. Bur. M. Bull. **2**:79 (Jan.) 1931.

of acute or chronic (chronic nuclear ocular paralysis or progressive ophthalmoplegia) superior poliencephalitis,[5] amyotrophic lateral sclerosis and progressive spinal muscular atrophy, tabes dorsalis, insular sclerosis, syringomyelia and other wasting maladies. Notably lacking in the literature is the consideration of congenital inferiority [6] and familial predisposition as worthy explanations for this disease. It has been argued that the integrity of the nervous system for periods of more than ten years precludes the possibility of congenital inferiority.[7] An ill defined hereditary or familial form of progressive bulbar paralysis of childhood has been described.[8] This form is usually accompanied by various stigmas of deviation and associated with upper facial involvement (lagophthalmos, etc.), and other symptoms of ophthalmoplegia, especially ptosis. Children of related parents have been afflicted. The duration of the process is relatively brief, owing to the tendency of the disease to attack successive generations at earlier ages than the preceding ones. Pathologic investigations suggest a degenerative lesion not unlike that of the adult form. That a congenital inferiority and a familial tendency may be etiologic factors in the true adult form of the disease is apparently shown by the following case.

REPORT OF A CASE

History.—N. M., a woman, married, a housewife, aged 66, was admitted to the neurology clinic of the University of Michigan Hospital on May 13, 1931, complaining of difficulty in speech and drooling of saliva. She had noticed the difficulty in speech nearly eight months before. Antirheumatic therapy had been instituted at that time by her family physician. The condition grew slowly worse, and in April, when swallowing became difficult, an otolaryngologist was consulted. He expressed the opinion that the dysarthria was the "result of some nervous lesion and due to a defect in articulation through defective use of the tongue." Examination of the larynx showed the vocal cords to be functioning normally, and sound production was good. There had never been any pain, nor had there been any weakness of the extremities. She had lost 10 pounds (4.5 Kg.) in weight since the onset of the illness.

The patient had always enjoyed good health. She did not marry until 48 years of age, and never became pregnant. The family history is striking. The patient's mother had a similar condition, and died at the age of 65 following a year's illness. Her mother's brother also died at about the same age with the disease, and his son likewise died in the fifth decade of life. There were no other nervous dis-

5. Church, A., and Peterson, F.: Textbook of Nervous and Mental Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1901.

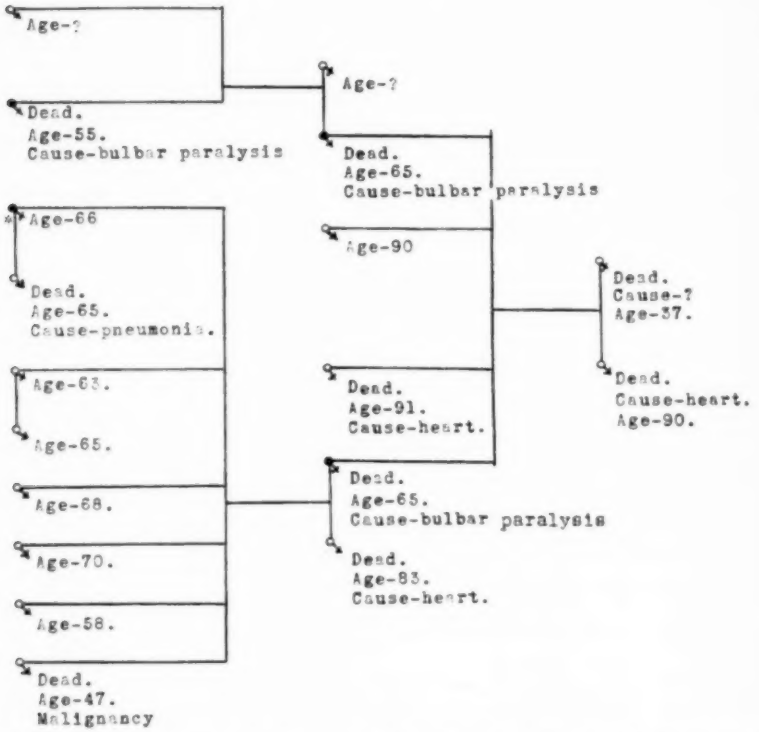
6. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1923, vol. 2, p. 1602.

7. Kino, F.: Ueber die Elektivität des bulbärparalytischen Prozesses, Ztschr. f. d. ges. Neurol. u. Psychiat. **119**:87, 1929.

8. Fazio: Riforma méd., 1892. Londe: Paralysie bulbaire progressive infantile et familiale, Rev. de méd. 10. Dec., 1893. Brissaud et Marie: Diplégie faciale totale avec paralysie glosso-laryngo-cervicale chez deux frères, Bull. méd., Paris **7**:1081, 1893.

eases in the family, and no members of the family except those mentioned had had the same condition (see chart).

Physical Examination.—The patient was of rather spare build. The hair was gray but abundant. There was an intelligent expression of the eyes. The mentality was not impaired. There was no asymmetry of the face, but the skin of the lower half seemed thin and inelastic, as if ironed out. The corners of the mouth drooped while the lower lip was everted and sagged, permitting abundant drooling of saliva. Arcus senilis was present. The nose and ears were normal. The teeth were all false. There were visible pulsations of the larger vessels of the neck. The lungs were normal. Respirations were slightly increased in rate. The heart



Genealogy in the case reported. The solid black symbols represent persons with bulbar paralysis.

was not enlarged, and there was no evidence of myocardial or valvular disease. The pulse was regular and of good quality with a rate of 102. The blood pressure was 135 systolic and 80 diastolic. The liver was palpable 2 cm. beneath the right costal margin. Neither it nor the gallbladder was tender. No other abdominal abnormalities were discernible. There were no atrophies or deformities of the extremities.

The pupils were regular and equal and reacted normally to light and in accommodation; the extra-ocular movements were normal. There was no nystagmus. The ocular fundi were normal. Neither angle of the mouth could be drawn back as far as normal, although both were retracted equally. The tongue did not

deviate to either side and could not be extended beyond the gingival margin. It was not definitely atrophied, but appeared spongy and showed constant fibrillary tremors. The speech was characteristically dysarthric. Deglutition was slow and laborious. The pharyngeal muscles were weakened, permitting the uvula to rise slowly, but always in the midline, on phonation. The larynx was not paralyzed. The deep tendon reflexes were normal, except for slightly but equally increased knee jerks. There was no Babinski sign or other pyramidal tract signs. Sensation was intact.

Laboratory Examination.—The hemoglobin was 87 per cent (Sahli); the red cells numbered 4,510,000 and the white cells, 5,500. A differential blood count and the results of morphologic studies of the blood were normal. Urinalysis and the Kahn test of the blood gave negative results.

Course.—Two months later, the patient was reexamined and was found to speak less well than when first seen. The dysarthria had progressed, and there were increased salivation and drooling. Deglutition was further impaired, which explained an additional loss of 5 pounds (2.3 Kg.) in weight. The facial muscles were weaker, and beginning atrophy of the tongue was apparent. The patient complained that the tongue felt as if it were "growing stiffer." The blood pressure remained unchanged; the pulse rate was 92, and there were occasional skipped beats. A few coarse râles were heard over the apex of the right lung, but the bases of the lungs were clear. The larynx appeared unchanged.

The patient was treated with small doses of ephedrine and atropine administered by mouth. Three months later, she reported that she was feeling stronger, and that the appetite was good, while deglutition was somewhat more difficult. The tongue had become further involved, and complete aphonia had developed. She expressed her thoughts in writing, which she did well.

It has been claimed by some [9] that progressive bulbar palsy is almost always followed by involvement of the pyramidal tracts, thereby constituting the syndrome of amyotrophic lateral sclerosis. I have had the opportunity of studying twenty cases that were considered as presenting pure forms of the disease without lateral sclerosis. Thirteen of the patients were women and seven were men. The average duration of symptoms prior to examination at the neurologic clinic was slightly over one year, the shortest being two months, the longest two years. In fifteen cases, the previous medical history was entirely without significance, and no cause for the malady was disclosed by the patient or discovered by the examiner. Two cases followed closely on the extraction of teeth.[10] One woman had been suffering with hay fever for some years prior to the development of the bulbar condition, while another attributed her misfortune to a "nervous breakdown" three years before. Trauma to the head preceded shortly the development of symptoms in one man, who in addition had latent syphilis, as evidenced by a positive Wassermann reaction of the blood but a negative

9. Leyden, E.: Ueber progressive amyotrophische Bulbärparalyse und ihre Beziehungen zur symmetrischen Seitenstrangsklerose, Arch. f. Psychiat. **8**:644, 1877.

10. Bailey, W.: Involvement of the Nervous System Following Extraction of Teeth, J. Nerv. & Ment. Dis. **13**:180 (Feb.) 1931.

reaction of the spinal fluid. In only one other case was the Wassermann reaction of the blood positive, and it is of more than passing interest to note that in this case, as in the previous one, the Wassermann reaction of the spinal fluid was negative. The Wassermann or Kahn reactions in the remaining eighteen patients were negative, and in none was there a positive history or clinical evidence of syphilis.

Older writers advocated dry cupping to the nape if there were associated pains in the head or neck. Soft food was given when swallowing was possible; otherwise an esophageal sound was employed. Silver nitrate was considered the most useful drug in early cases, and gold salts were recommended. It was known then as now that benefit can be obtained from the local faradization of the palate, tongue and hypoglossal nerves, but that galvanization by means of a strong continuous current is more effective. Phosphorus, strychnine, potassium bromide and the iodide of iron were believed to be useless, if not injurious.

The treatment formerly was obviously palliative. It is not yet as successful as it is hoped that it may become. However, highly beneficial results are obtained with atropine, which serves the double purpose of stimulating the heart and checking salivary hypersecretion. Ephedrine and strychnine are usually helpful. The value of endocrine therapy in asthenic bulbar paralysis, in which multiglandular pathologic changes commonly occur, strongly suggests its use in the progressive form of bulbar palsy. There is much to be said in favor of gastrostomy,[11] which not only affords the involved muscles rest, which is desirable, but reduces to a minimum the likelihood of intercurrent maladies and pulmonary accidents.

SUMMARY

I have reported a classic case of true progressive bulbar paralysis presenting a congenital and familial background. The disease appears to be transmitted as a recessive, non-sex-linked mendelian trait. Two members of the F_1 generation and two (cousins) of the F_2 generation were afflicted.

In conclusion, it is my opinion that, although bulbar palsies are associated with and often form a dominant portion of the symptom complexes of various degenerative and sometimes inflammatory diseases, true progressive bulbar paralysis may and does exist as a separate and distinct entity. The long and varied list of heretofore reported etiologic factors serves only to condemn them. The rarity of the disease, its failure to occur commonly as a result of any of these factors, and particularly the degenerative, noninflammatory type of pathologic change point to a predisposing hereditary or familial medullary inferiority.

11. Seigi, M., and Harzbecker: Ueber den Erfolg einer künstlichen Magenfistel bei progressiver Bulbärparalyse, Deutsche med. Wchnschr. **55**:272 (Feb. 15) 1929.

LECITHIN AND CHOLESTEROL IN CEREBROSPINAL SYPHILIS INCLUDING DEMENTIA PARALYTICA AND TABES

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Studies of the occurrence of lecithin and cholesterol in the blood and spinal fluid of patients suffering from the various forms of syphilis of the central nervous system show very different results. Active interest in these substances during the past decade has made us feel more and more the necessity for additional investigation. We have now completed analyses in seventy-eight cases (including tabes, cerebrospinal syphilis and dementia paralytica). Though this is too small a number for conclusive deductions, the results may be helpful.

The analytic methods employed were essentially those published in 1928 and 1929.[1] All our patients were inmates of the Manhattan State Hospital. The blood and spinal fluid were drawn in the morning before breakfast. We studied four groups of patients:

I. Those suffering from cerebrospinal syphilis and dementia paralytica (untreated).

II. Those affected with tabes (untreated).

III. Those suffering from cerebrospinal syphilis, tabes and dementia paralytica at various stages of treatment.

IV. Those in whom the involvements were like those in group I, but in whom blood and spinal fluid were drawn before treatment was instituted and again after a course of treatment.

Table 1 gives a summary of the results obtained. The average values for lecithin ranged from 242 ± 27 to 265 ± 34 mg. per hundred cubic centimeters of whole blood. There is an interesting difference between the treated and untreated patients. Comparison between the results for

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1. Krasnow, F., and Rosen, A. S.: Proc. Soc. Exper. Biol. & Med. **26**:67, 1928; J. Lab. & Clin. Med. **14**:967, 1929. Rosen, I., and Krasnow, F.: Lecithin and Cholesterol Studies in Dermatophytosis, Arch. Dermat. & Syph. **23**:132 (Jan.) 1931.

TABLE 1.—*Summary of the Lecithin and Cholesterol Content of Whole Blood in Dementia Paralytica, Tabes and Cerebrospinal Syphilis*

Group	Description of Cases	Number of Cases	Average Lecithin, Mg. per 100 Cc. Whole Blood	Average Cholesterol, Mg. per 100 Cc. Whole Blood
	Normal	27	242 ± 22	171 ± 16
I	Cerebrospinal syphilis and dementia paralytica (untreated)	30	250 ± 23	179 ± 27
II	Tabes (untreated)	18	250 ± 20	171 ± 23
III	Cerebrospinal syphilis and dementia paralytica (treated)	30	265 ± 34	160 ± 27
IV	Cerebrospinal syphilis, tabes and dementia paralytica			
	A, before treatment	20	243 ± 26	162 ± 27
	B, after treatment	..	250 ± 22	172 ± 26
I + IV A		50	247 ± 25	172 ± 28
III + IV B		50	259 ± 22	165 ± 27

TABLE 2.—*Gradations in the Lecithin Content of the Whole Blood in Cerebrospinal Syphilis, Tabes and Dementia Paralytica*

Group	Description of Cases	Total Number	Per Cent of Cases Showing Lecithin Content of Whole Blood		
			Below 242 − 22 Mg. per 100 Cc.	Within 242 ± 22 Mg. per 100 Cc.	Above 242 + 22 Mg. per 100 Cc.
I	Cerebrospinal syphilis and dementia paralytica (untreated)	30	10	67	23
II	Tabes (untreated)	18	5	61	33
III	Cerebrospinal syphilis and dementia paralytica (treated)	30	13	40	47
IV	Cerebrospinal syphilis, tabes and dementia paralytica				
	A, before treatment	19	16	68	16
	B, after treatment	20	5	55	40
I + IV A		50	12	67	21
III + IV B		50	10	46	44

TABLE 3.—*Gradations in Cholesterol Content of Whole Blood in Cerebrospinal Syphilis, Tabes and Dementia Paralytica*

Group	Description of Cases	Total Number	Per Cent of Cases Showing Cholesterol Content of Whole Blood		
			Below 171 − 16 Mg. per 100 Cc.	Within 171 ± 16 Mg. per 100 Cc.	Above 171 + 16 Mg. per 100 Cc.
I	Cerebrospinal syphilis and dementia paralytica (untreated)	30	23	43	33
II	Tabes (untreated)	18	33	44	22
III	Cerebrospinal syphilis and dementia paralytica (treated)	30	43	47	10
IV	Cerebrospinal syphilis, tabes and dementia paralytica				
	A, before treatment	20	45	30	25
	B, after treatment	20	25	55	20
I + IV A		50	32	38	30
III + IV B		50	36	50	14

TABLE 4.—*Cholesterol and Lecithin Content of Whole Blood and Spinal Fluid in Cerebrospinal Syphilis and Dementia Paralytica*

20 Cases

Serial Number	Cholesterol, Mg. per 100 Cc. Whole Blood	Lecithin, Mg. per 100 Cc. Whole Blood	Cholesterol in Spinal Fluid
1	159	312	++++
2	176	262	++++
3	136	260	++++
4	156	255	++++
5	133	257	++++
6	139	230	++++
7	154	277	++++
8	150	252	++++
9	140	260	++++
10	132	375	++++
11	196	287	++++
12	266	332	++++
13	159	252	++++
14	167	280	++++
15	182	277	No spinal fluid
16	151	257	++++
17	175	285	++++
18	176	275	++++
19	161	270	++++
20	158	277	++++

TABLE 5.—*Cholesterol and Lecithin Content of Whole Blood in Cerebrospinal Syphilis and Dementia Paralytica*

30 Untreated Cases

Serial Number	Age	Serology Findings				Cholesterol, Mg. per 100 Cc. Whole Blood	Lecith'n, Mg. per 100 Cc. Whole Blood
		Cells	Globulin	Blood	Spinal Fluid		
9	41	7	3+	3+	4+	152	237
6	62	45	3+	4+	4+	155	252
8	36	16	+	4+	3+	144	287
47	36	5	2+	4+	4+	160	232
22	32	27	4+	4+	4+	154	227
33	48	17	3+	4+	4+	193	222
32	60	27	4+	3+	3+	169	250
4	48	10	+	4+	4+	150	265
38	41	..	...	4+	4+	181	282
31	44	25	3+	3+	3+	170	252
29	60	23	2+	3+	3+	186	247
39	44	14	2+	3+	4+	219	262
41	33	5	0	4+	4+	174	245
44	35	24	3+	4+	4+	226	300
46	57	16	2+	3+	4+	151	257
12	44	..	+	3+	3+	146	207
23	34	18	2+	3+	3+	160	230
24	42	7	+	3+	3+	184	250
15	59	10	+	4+	4+	199	255
10	40	2	+	4+	4+	207	237
27	40	2	+	4+	4+	200	212
11	38	15	2+	4+	4+	180	240
26	38	15	2+	4+	4+	166	250
13	57	9	+	4+	4+	200	285
14	30	17	2+	4+	4+	191	280
51	44	30	3+	4+	4+	171	250
52	41	..	2+	4+	4+	216	255
25	18	..	+	3+	3+	138	205
37	55	Negative	Negative	4+	Negative	162	242
40	43	Negative	+	4+	Negative	261	290

TABLE 6.—*Cholesterol and Lecithin Content of Whole Blood in Tabes*

18 Untreated Cases

Serial Number	Age	Serology Findings				Cholesterol, Mg. per 100 Cc. Whole Blood	Lecithin, Mg. per 100 Cc. Whole Blood
		Cells	Globulin	Blood	Spinal Fluid		
21	43	Negative	Negative	4+	4+	160	220
3	36	3	+	3+	4+	151	270
7	50	29	2+	4+	4+	156	207
18	52	20	2+	4+	4+	154	267
17	38	3	+	4+	4+	195	247
20	57	7	3+	3+	3+	160	245
19	72	13	+	Negative	4+	153	232
34	41	15	4+	3+	3+	147	230
30	50	33	4+	3+	3+	166	250
43	50	..	...	...	...	182	270
28	39	11	+	4+	4+	176	252
42	39	..	...	...	...	187	275
1	34	6	2+	4+	4+	134	252
36	34	..	...	...	...	151	232
2	34	5	2+	4+	4+	180	275
35	34	..	...	...	...	220	237
45	42	30	4+	4+	4+	199	287
16	36	16	3+	3+	3+	214	272

TABLE 7.—*Cholesterol and Lecithin Content of Whole Blood in Cerebrospinal Syphilis and Dementia Paralytica*

30 Treated Cases

Serial Number	Age	Serology Before Treatment				Serology After Treatment				Cholesterol, Mg. per 100 Cc. Whole Blood	Lecithin, Mg. per 100 Cc. Whole Blood
		Cells	Globulin	Blood	Spinal Fluid	Cells	Globulin	Blood	Spinal Fluid		
12	56	41	4+	4+	3+	0	+	4+	4+	140	240
13	40	17	3+	4+	4+	8	1+	3+	4+	110	215
7	48	200	3+	4+	4+	..	...	...	...	131	217
8	34	75	3+	4+	4+	5	+	3+	3+	143	217
4	41	20	3+	4+	4+	10	2+	3+	3+	157	285
6	42	20	1+	4+	4+	..	...	...	...	172	282
2	43	13	4+	4+	4+	3	+	4+	4+	147	232
1	55	23	3+	4+	4+	8	1+	4+	4+	190	282
10	40	30	3+	4+	4+	..	...	...	...	181	210
3	49	20	2+	4+	4+	3	1+	4+	+	180	232
1	.....									159	312
2	.....									176	262
3	.....									136	260
4	.....									156	255
5	.....									133	257
6	.....									139	230
7	.....									154	277
8	.....									150	272
9	.....									140	260
10	.....									132	375
11	.....									196	287
12	.....									266	332
13	.....									159	252
14	.....									167	280
15	.....									182	277
16	.....									151	257
17	.....									175	285
18	.....									176	275
19	.....									161	270
20	.....									158	277

groups I and II, on the one hand, and group III, on the other, seems to indicate a distinct rise in lecithin after treatment. A similar rise was obtained for *B* of group IV. Again group I + IV *A* showed a general

TABLE 8.—*Cholesterol and Lecithin Content of Whole Blood in Cerebrospinal Syphilis, Tabes and Dementia Paralytica*

20 Cases, Before and After Treatment*

		Serology Before Treatment						Serology After Treatment				
Serial Number	Age	Cells	Globulin	Blood	Spinal Fluid	Cholesterol, Mg. per 100 Cc. Whole Blood	Lecithin, Mg. per 100 Cc. Whole Blood	Cells	Globulin	Blood	Spinal Fluid	Comment
5	57	11	+	4+	4+	150	230					
41	..	..	...	...	...	153	232	7	+	3+	3+	Improved
1	54	18	2+	4+	4+	131	237					
24	..	..	...	...	...	181	295	15	3+	4+	4+	Improved
8	43	7	2+	4+	4+	197	250					
26	..	..	...	...	...	175	250					
7	33	10	+	4+	4+	195	232					
39	..	..	...	...	...	158	270	10	+	4+	4+	Improved
4	45	17	+	4+	4+	129	250					
28	..	..	...	...	...	132	225					
45	..	..	...	...	...	...	...	5	+	4+	4+	Improved
6	50	32	2+	4+	4+	143	220					
20	..	..	...	...	...	150	185	5	+	4+	4+	Improved
10	38	35	3+	4+	4+	196	275					
21	..	..	...	...	...	201	277	18	3+	3+	3+	Improved
3	45	15	+	3+	3+	130	202					
44	..	..	...	...	...	140	240					
19	35	149	3+	4+	4+	138	247					
36	..	..	...	...	...	182	267	..	...	...	...	Improved
18	29	130	2+	4+	4+	142	217					
29	..	..	...	...	...	190	257					
33	..	..	...	...	...	...	...	..	...	...	4+	Improved
16	27	3+	4+	4+	4+	142	200					
40	..	..	...	...	...	160	267	4	+	2+	...	Improved
14	48	18	2+	4+	4+	179	250					
43	..	..	...	...	...	168	250	Neg.	Neg.	4+	4+	Improved
13	37	32	3+	4+	4+	170	245					
29	..	..	...	...	...	160	232					
32	..	..	...	...	...	...	...	10	+	4+	4+	Improved
9	..	15	2+	4+	4+	155	227					
27	..	..	...	...	...	160	230					
30	..	..	...	...	...	...	...	6	4+	3+	2+	Improved
17	48	16	3+	4+	4+	164	260					
46	..	..	...	...	...	231	275	..	...	...	...	Improved
25	48	15	+	3+	4+	222	295					
34	..	..	...	...	...	181	272	8	+	2+	3+	Improved
14a	35	300	3+	3+	3+	164	None					
37	..	..	...	...	...	180	232					
12	42	13	+	4+	4+	170	227					
15	..	..	...	...	...	146	230					
31	..	..	...	...	...	...	...	9	+	3+	...	Improved
2	53	2	+	+	Neg.	193	300					
38	..	..	...	...	...	238	295					
11	27	0	0	4+	4+	138	262					
23	..	..	...	...	...	166	225					
35	..	..	...	...	...	...	...	5	+	4+	Neg.	Improved

* Upper figures of cholesterol and lecithin are before treatment; lower figures are after treatment.

average of 247 ± 25, which is distinctly lower than the average for the treated groups III + IV *B*.

Table 2 lists the results in a somewhat different way. It may be seen that a large number of patients (more than 50 per cent of groups

I, II and IV) actually showed a normal content of blood lecithin. The treated patients, as classified here, showed increased lecithin. A comparison of the results for groups I and III and group IV *A* and *B* indicates this point.

For cholesterol (tables 1 and 3) the average values ranged from 160 ± 27 to 179 ± 27 mg. per hundred cubic centimeters of whole blood. There appears to be no regularity in the changes produced. Thus, in the treated patients of group III the average cholesterol value was relatively low, whereas in those of group IV *B* it was normal. It is noticeable that in table 3 (groups II, III and IV *A*) there is a high percentage of cases with the cholesterol content below the low normal. We cannot now explain why so many treated patients had a low cholesterol content of the blood. The large number of patients that showed values above the high normal in group I is also striking.

These studies on the blood were supplemented with analyses of the spinal fluid. Thus far all our attempts to find lecithin in this fluid have been unsuccessful. Very small amounts of cholesterol were found in all spinal fluids examined. The results listed in table 4 are roughly quantitative: + + + + stands for a definite green color. No correlation with the cholesterol content of the blood was apparent. The technic for the determination of cholesterol in the spinal fluid was that used for its analysis in blood.[2] Before proceeding, however, it was necessary to concentrate the spinal fluid by evaporating 10 cc. to 1 cc.

As may be seen from tables 5, 6, 7 and 8, the cell count, globulin content and serology of the spinal fluid and the serology of the blood were determined in practically all cases. We have been unable to show any relationship between these results and the cholesterol or lecithin content of the blood or spinal fluid.

2. Rosen and Krasnow (footnote 1, second reference).

CALCIUM CONTENT OF THE BRAIN AND ITS DISTRIBUTION IN VARIOUS REGIONS DURING DIALLYLBARBITURIC ACID NARCOSIS

AN EXPERIMENTAL STUDY

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Previous calcium studies in sleep have led to the conclusion that hypnotic sleep provoked by diallylbarbituric acid is associated with a decrease of calcium in both blood and cerebrospinal fluid.[1] This experimental investigation is concerned with the calcium content of the brain and also specifically with the distribution of calcium in certain areas of the brain in a series of animals killed during sleep and in another series killed in the waking state.

Calcium has been chosen as the subject of study in preference to other blood constituents on account of the investigations referring to its pharmacodynamic effect on the brain and to the particular rôle it is alleged to play in sleep. Pharmacologic studies, among which those concerned with calcium are preeminent, have contributed greatly to the much debated problem as to whether sleep is regulated by specific sleep centers. The common character of these pharmacologic contributions lies in the demonstration that certain drugs appear to have specific pharmacodynamic effects on various areas of the brain. Thus, scopolamine, which is known to be slightly effective in herbivorous animals, easily induced sleep in these animals when the cortex was either removed [2] or functionally inhibited by sodium bromide.[3] Apomorphine [4]

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1. Katzenelbogen, S.: The Blood Electrolyte Changes in Narcosis, with Special Reference to Calcium and Potassium: An Experimental Study, Arch. Neurol. & Psychiat. **24**:525 (Sept.) 1930; The Distribution of Calcium Between Blood and Cerebrospinal Fluid in Sleep Induced by Diallylbarbituric Acid: An Experimental Study, ibid. **27**:154 (Jan.) 1932.

2. Meltes, J.: Studien über den Angriffspunct von Schlafmitteln, Wien. klin. Wchnschr. **39**:962, 1926.

3. Pick, E. P.: Pharmakologie des vegetativen Nervensystems, Deutsche Ztschr. f. Nervenh. **106**:238, 1928.

4. Morita, S.: Untersuchungen an grosshirnlosen Kaninchen, Arch. f. exper. Path. u. Pharmakol. **78**:208, 218 and 223, 1915.

produced sleep in rabbits only after the removal of the cortex and the striate bodies. The inference derived from these observations is that the hypnotic function of the subcortical region is counteracted by the stimulation emanating from the cortex and the striate bodies. Further attempts to investigate the respective rôle of the cortex and the subcortical region in sleep have been made in the following studies: Caffeine, as a cortical stimulant, easily awakened animals in which sleep was produced with chloral hydrate. In decerebrated animals caffeine proved to be inactive. In the same conditions, that is, when sleep is induced in decerebrated animals with chloral hydrate, drugs such as epinephrine or ephedrine, considered to be subcortical stimulants, have a pronounced waking effect.[5]

The studies so far recorded suggest that cortical activity interferes with the hypnotic function of the subcortical areas. Other pharmacologic investigations point more specifically to the thalamic and hypothalamic regions as the seat of sleep centers. Thus, Keeser and Keeser[6] have demonstrated that preparations of the barbituric acid group, introduced into the general circulation, accumulated mainly in the thalamus. Only a small proportion could be detected in the striate bodies, and none could be found in other parts of the brain. In passing, it may be mentioned that in contrast to the hypnotics of the barbital group, which in the classification of Pick[7] are considered as thalamic hypnotics, ether, chloroform, alcohol, chloral hydrate, paraldehyde and bromides are classified as cortical narcotics or hypnotics. The combined administration of both cortical and thalamic hypnotics has been proved to yield distinct synergic effects in experimental studies on animals.[8]

Calcium appears to exercise distinctly different pharmacodynamic effects on the cortical and subcortical parts of the brain. Thus, it has been observed that narcosis induced in animals by means of magnesium rapidly surrenders to intravenous injections of calcium.[9] After the

5. Airila: Arch. internat. de pharmacodyn. et de thérapie **23**:453, 1913. Pick (footnote 3). Morita (footnote 4).

6. Keeser, E., and Keeser, T.: Ueber die Lokalisation des Veronals, des Phenyläthyl und Diallylbarbitursäure im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**:251, 1927; Ueber den Nachweis von Caffein, Morphin und Barbitursäure Derivaten im Gehirn, ibid. **127**:230, 1927.

7. Pick, E. P.: Ueber Schlaf und Schlafmittel, Wien. klin. Wchnschr. **40**: 634, 1927.

8. Molitor, H., and Pick, E. P.: Verstaerkte Schlafmittel-Wirkung durch gleichzeitige Behandlung verschiedener Hirnteile, Arch. f. exper. Path. u. Pharmakol. **115**:318, 1926.

9. Mansfield: Experimental Investigation on the Nature and Promises of Tetany Therapy with Magnesium Sulphate, München. med. Wchnschr. **62**:208, 1915.

excision of the cortex and striate bodies, magnesium still held its property of inducing narcosis, whereas calcium had lost its counteracting effect.[3] From these experiments it may be inferred that calcium has a stimulating effect on the cortex, on the striate bodies or on both. On the other hand, certain investigations bring to the fore the concept that calcium has a depressing effect on the thalamic region. In this respect reference has been made to the hypnotic effect of calcium on thalamic animals; that is, on animals in which the cortex and striatum have been removed.[3] The pharmacodynamic effects of calcium on the thalamic and hypothalamic region are further emphasized by the experimental studies of Demole. This author[10] has induced sleep in cats by intracerebral injections of calcium chloride, namely, into the hypothalamic region. With 0.25 mg. of chloride of calcium sleep lasted from thirty to sixty minutes; with 2 mg. of calcium chloride sleep was of three hours' duration. The solution of calcium chloride was colored and could therefore be located on anatomic examination. It was shown that in the twenty-nine cats that slept soundly calcium chloride proved to be located chiefly in the para-infundibular region, which is therefore considered by the experimenter as the sleep area. The work of this author was suggested by the hypothesis of Cloetta,[11] according to which decrease of calcium in the blood during sleep due to hypnotics would be accompanied by a shift of calcium from the blood into the brain tissue. The striking results obtained by Demole may be evaluated as supporting Cloetta's theory, as the introduction of calcium into the brain and the consequent increase of its concentration in the brain tissue had invariably induced sleep. On the other hand, one also feels justified in asserting that the data just mentioned only illustrate the pharmacodynamic effect of calcium introduced into the hypothalamic region. It would therefore seem, in my judgment, questionable whether the otherwise extremely interesting study of Demole may be used at all in the discussion pro and con of Cloetta's teaching. It seemed to me, therefore, more promising to attack the problem from the following angle: Instead of introducing calcium into the cerebral tissue, I attempted to follow the behavior of calcium in the whole brain and in its various areas during sleep.

METHOD OF INVESTIGATION

The study was carried out on cats in which sleep was induced by diallylbarbituric acid. After the duration of sleep for from eighteen to twenty-two hours and while in profound sleep, the animals were killed and the brains immediately removed. In a series of twenty sleep experiments calcium was

10. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

11. Cloetta and Thomann: Chemisch-physikalische Untersuchungen zur Theorie der Narkose, Arch. f. exper. Path. u. Pharmakol. **103**:260, 1924.

determined in the whole brain. This investigation was supplemented by fifteen control experiments performed under similar conditions, except that the animals were not given any drug and were killed in the waking state.

In another series of fifteen sleep experiments, the removed brains were cut in order to determine the calcium in each of the following regions: (1) right frontal; (2) left frontal; (3) right parietal; (4) left parietal; (5) hypothalamic region, including the optic chiasm, infundibulum, tuber cinereum and mammillary bodies—from the chiasm to the root of the third nerve; (6) cerebellum and medulla oblongata taken together.

Equal portions in each of these sections were used for the analysis. Again, a similar control study was carried out in ten cats killed in the waking state. The removed brains were cut into the sections just mentioned, and the analysis of calcium was carried out in exactly the same way.

Determination of Calcium in the Brain.—Calcium in the Whole Brain: The freshly removed brain was washed with water in order to free it from clots of blood. Then it was blotted to remove excess moisture, weighed and placed in alcohol (95 per cent) for from one to two days. The fixed brain was cut into fine pieces and placed in a wide mouthed bottle at a temperature of from 100 to 110 C. for about two days until a constant weight was reached. The alcohol used for fixation was evaporated on the water bath, and the residue desiccated at the same temperature to a constant weight. The total weight of the dry brain was obtained by adding the weight of this residue to the weight of the dry brain. Calcium was determined in both the desiccated brain and the residue. The calcium content of the latter was added to the calcium content of the whole brain. Five-tenths gram of the desiccated brain tissue was used for analysis.

Calcium in Various Sections of the Brain: After fixation in alcohol for about twenty-four hours, the brain was cut into the sections already mentioned. These were again placed in fresh alcohol for a period of from one to two days. Then they were cut into fine pieces and desiccated at a temperature of from 100 to 110 C. to a constant weight. For the determination of calcium in each of the sections, 0.2 Gm. of the desiccated brain tissue was used.

Method of Analysis.—The dried brain is ashed as follows: Place a platinum crucible (height, 25 mm.; diameter at the top, 35 mm.) containing the dried brain in a large porcelain crucible (height, 48 mm.; diameter at the top, 50 mm.). Heat carefully above a low flame until gases and fumes cease to evolve, then raise the temperature until the platinum crucible reaches a red heat. The ashing is complete when all traces of carbon are burned away, which requires about two hours. Allow the material to cool.

Transfer the crucible containing the ash to a hot water bath; add 2 cc. of approximately tenth-normal hydrochloric acid, and allow the mixture to evaporate to dryness. The hydrochloric acid treatment is repeated twice.

Transfer the treated ash to a 15 cc. graduated centrifuge tube in the following way: add 2 cc. of tenth-normal hydrochloric acid and transfer quantitatively, with the aid of a rubber policeman, to a small washed filter (funnel, 27 mm. in diameter at the top, fitted with a Whatman filter paper no. 40, 55 mm.). Collect the filtrate in a centrifuge tube. Wash the crucible with three portions (from 1 to 2 cc.) of tenth-normal hydrochloric acid; the filter is washed finally with tenth-normal hydrochloric acid until the total volume reaches 8 cc.

Allow the clear hydrochloric acid solution to cool. Add 1 drop of methyl red indicator. Add drop by drop approximately five-tenths normal sodium hydroxide until just alkaline, then adjust to a p_H of from 4.8 to 5 with tenth-normal hydrochloric acid. Dilute to 10 cc. with water.

Add 5 cc. of saturated ammonium oxalate (previously adjusted to a p_H of from 4.8 to 5) to the centrifuge tube, cover with a rubber stopper and mix by shaking; allow to stand for three hours, and then centrifugate for ten minutes.

Pour off the supernatant fluid. Set the tube in a rack with the mouth of the tube resting on a pad of filter paper, and allow it to drain for five minutes.

Wash the precipitate with 5 cc. of ammonium hydroxide (2 cc. of concentrated ammonium hydroxide to 100 cc. of water). Centrifugate for ten minutes and remove the supernatant fluid. Allow the tube to drain as already indicated.

TABLE 1.—*Calcium in the Whole Brain*

Experiment	Sleep, Mg. per 100 Gm.	Control, Mg. per 100 Gm.
1	5.8	6.2
2	5.6	6.2
3	7.5	5.0
4	4.4	5.6
5	5.2	6.7
6	5.9	6.4
7	5.4	5.0
8	6.5	4.9
9	6.1	6.1
10	7.4	5.8
11	6.0	7.1
12	5.1	5.6
13	4.8	6.0
14	6.6	5.4
15	5.4	4.8
16	4.8	
17	4.0	
18	5.6	
19	6.5	
20	4.6	
Range	4.0 to 7.5	4.8 to 7.1
Average	5.66	5.79

Dissolve the precipitate in 2 cc. of approximately normal sulphuric acid; place in a hot water bath for about three minutes; titrate with hundredth-normal potassium permanganate.

Calculation: It was calculated that 1 cc. of potassium permanganate is equivalent to 0.2 mg. of calcium.

Errors of the Method.—From duplicate determinations and the analysis of standard calcium solutions the errors for this procedure were found to be within 0.5 cc. of hundredth-normal potassium permanganate or 0.01 mg. of calcium in the sample used.

RESULTS

The calcium measurements in the whole brain are tabulated in table 1. It may be seen that in the twenty sleep experiments the brain calcium ranges between 4 and 7.5 mg. per hundred grams, the average being 5.66 mg. In the control experiments the range lies within 4.8 and 7.1 mg. per hundred grams, with an average of 5.79 mg.

The calcium determinations in the particular sections of the brain, in both sleep and control experiments, are given in table 2. This table shows that the range and the average of the calcium figures obtained in the hypothalamic sections of the fifteen narcotized animals are higher than the range and average of the calcium contents of any other region of the brain. The control study displays essentially the same feature; that is, the highest range and average of the calcium contents are to be found in the hypothalamus.

TABLE 2.—*Calcium in Various Regions of the Brain* *

	Hypothalamic		Right Parietal		Left Parietal		Right Frontal		Left Frontal		Cerebellum, Medulla Oblongata	
Experiment	Sleep	Control	Sleep	Control	Sleep	Control	Sleep	Control	Sleep	Control	Sleep	Control
1	42	33	37	26	48	27	41	33	42	30	41	27
2	48	37	38	28	41	31	44	33	40	28	43	39
3	35	40	30	34	33	37	36	39	34	32	31	33
4	32	38	32	34	39	43	35	47	35	34	35	44
5	33	39	35	33	30	33	31	35	33	32	29	30
6	51	38	30	34	39	30	37	37	25	36	34	31
7	35	41	27	38	27	38	33	43	32	38	28	37
8	37	55	29	39	31	40	35	39	30	50	27	39
9	38	36	41	36	37	36	37	38	39	36	43	35
10	49	40	39	41	39	37	39	35	38	39	33	39
11	38		33		38		39		36		30	
12	39		38		37		37		36		35	
13	32		32		39		36		39		31	
14	34		48		36		40		37		49	
15	43		35		43		42		34		43	
Range	32 to 51	33 to 55	27 to 48	26 to 41	27 to 48	27 to 43	31 to 44	33 to 47	25 to 42	28 to 50	27 to 49	27 to 44
Average	39.1	39.7	34.9	34.3	34.2	35.2	36.8	37.9	36.0	35.2	35.1	34.5

* All the figures are in milligrams per hundred grams of dried brain.

COMMENT

The original topic of this study was to investigate the modifications calcium might undergo in the brain, taken as a unit, during sleep. It was thought that such an inquiry would put to an experimental test the hypothesis of Cloetta and Thomann regarding the displacement of calcium from blood into the cerebral tissue during sleep.[11] In view of the fact that no sufficient data could be found in the literature as to the calcium content of the brain, taken as a whole, of cats killed in the waking state, the sleep experiments were complemented by a control study. A comparative scrutiny of the figures obtained in the sleep and control experiments of brain calcium brings out the fact that there are to be found variations in the calcium content of the brain, of nearly the same magnitude, in both the narcotized and the control animals. Thus, calcium was shown to range from 4 to 7.5 mg. per hundred grams, with an average of 5.66 mg., in sleep and from 4.8 to 7.1 mg., with an average of 5.79 mg., in the waking state (table 1).

These negative results, which apparently do not corroborate the aforementioned hypothesis, have led to a further inquiry, namely, into the distribution of calcium in different regions of the brain during sleep. Here, again, the results obtained in the sleep experiments may be adequately evaluated when compared with the findings in the control experiments. The calcium concentration, expressed in milligrams for each 100 Gm. of dry brain tissue in each of the specified brain areas, is nearly the same in the narcotized and in the control animals. It seems, therefore, safe to state, on the strength of the data so far recorded, that neither the concentration of calcium in the whole brain nor its distribution in various brain areas undergoes marked changes during sleep due to hypnotics (tables 1 and 2). Negative results of this study contain, however, one striking feature: that is, that calcium is found to be in a higher concentration in the hypothalamic region than in any other region. This holds true in cats killed during sleep as well as in those killed in the waking state (table 2). This seems to be significant in the light of the following data: The experimental studies previously reviewed have shown that calcium had a hypnotic effect when it appeared to affect the thalamic,[3] and more specifically the para-infundibular, region.[10] Moreover, it should be noted that Hess [12] had induced sleep in cats with ergotamine injected into the third ventricle. He also succeeded in provoking sleep by a special procedure which consisted in introducing electrodes into the brain.[13] Sleep was observed in cats in which the electric stimulation was applied to the paraventricular area (third ventricle). On the other hand, combined clinical and anatomicopathologic studies in man suggest that the hypothalamic region is intimately involved in sleep. Thus, in Economo's opinion, lesions in the region of the third ventricle are responsible for disorders of sleep in epidemic encephalitis. From the statistical study of Righetti [14] it follows that tumors situated near the thalamus and the third ventricle are more likely to cause hypersomnia than tumors located in any other region.

Weisenburg [15] has noted either a dull, stupid mentality or a decided tendency to drowsiness or somnolence in sixteen of thirty cases of tumors of the third ventricle. In the light of these data, pointing, on the one hand, to the depressing effect of calcium on the thalamic and

12. Hess, W. R.: Ueber die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen, Schweiz. Arch. f. Neurol. u. Psychiat. **16**:35 and 285, 1925.

13. Hess, W. R.: Die Funktionen des vegetativen Nervensystems, Klin. Wchnschr. **9**:1009, 1930.

14. Righetti, R.: Contributo clinico e anatomo-patologico allo studio dei gliomi cerebrali, Riv. di pat. nerv. **8**:241, 1903.

15. Weisenburg, T. H.: Tumors of the Third Ventricle, with the Establishment of a Symptom-Complex, Brain **33**:236, 1911.

hypothalamic region, and, on the other, to the apparent connection between this cerebral area and sleep, the finding of a high calcium content in the hypothalamus, as compared to other cerebral areas, suggests that calcium may take a certain part in the hypersomnic function ascribed to the hypothalamus.

SUMMARY AND CONCLUSIONS

1. A review of the literature referring to certain experimental studies on animals and to clinical and anatomicopathologic observations on man suggests the following: (1) calcium has a depressing effect on the thalamic and hypothalamic region; (2) this cerebral area plays a certain rôle in drowsiness, somnolence and sleep.

2. This study is concerned with the determination of the calcium content of the brain and with the distribution of calcium in different areas of the brain in cats during sleep.

3. Sleep was induced by diallylbarbituric acid in twenty cats. The animals were killed while in deep sleep, and the brains were immediately removed for the determination of calcium.

4. Since the calcium content of the whole brain showed no specific deviation from that of the fifteen control animals, calcium was determined in another series of fifteen sleep experiments in the following regions: right and left frontal; right and left parietal; cerebellum and medulla oblongata taken together; hypothalamic region, from the optic chiasm to the root of the third nerve.

5. The calcium contents of the whole brain removed from the narcotized and control animals range within nearly the same limits.

6. In the hypothalamic region the calcium content was found to be higher than in any of the other brain areas, in both the narcotized and control animals.

7. This finding nevertheless suggests that calcium may play a certain rôle in the function of the hypothalamic region.

Clinical Notes

INTRACRANIAL CHORDOMA

Report of a Case

HERMAN SELINSKY, M.D., NEW YORK

Virchow,[1] in 1846, while engaged in a study of the formation of the base of the skull, occasionally noted a jelly-like excrescence at the clivus (spheno-occipital synchondrosis). This anatomic anomaly he termed "ecchondrosis physaliphora." Its significance as a notochordal remnant was pointed out by Muller[2] in 1858. Ribbert[3] confirmed this conception by interesting experimental work, and suggested the term "chordoma" for the tumefaction derived from the ecchondrosis. This notochordal remnant occurred in 2 per cent of the autopsy material. Stewart and Morin[4] more recently have estimated its frequency as 1.5 per cent in their autopsy material.

This vestigial remnant may rarely undergo a transition into a growth of malignant character. The tumor has been found most frequently at the spheno-occipital and sacrococcygeal synchondroses. It may, however, develop along the spine between these two points from the notochord remnant persisting at the intervertebral disk.[5] The neoplastic growth is strikingly characterized by its local destructive effect on bone. The tumor appears as a white jelly-like mass, with a smooth surface and nodular protuberances. It is cystic, containing mucoid material. The microscopic appearance is uniform, with large and small vacuolated cells, which have been shown to contain glycogen.

This report is concerned chiefly with the chordomas arising within the intracranial cavity. Intracranial chordomas may be divided, according to their site, into clivus chordoma, hypophyseal chordoma and, less commonly, nasopharyngeal chordoma. Some of these growths have been reported to have an intracranial process with extension of the neoplastic mass down into the nasopharynx. In several cases of this type, the condition was detected by examination of the nasopharynx, and the tumor was removed.[6]

The early symptoms are generally those of increased intracranial pressure, such as headache, vertigo, nausea and vomiting, and progressive impairment of vision. Papilledema or optic atrophy may be found. Later there may occur paralysis of the various cranial nerves. Seldom is any evidence of pituitary disorder noted. Roentgenographic examination of the skull frequently reveals a destructive process in the vicinity of the lesion. In the case reported here the tumor is of the type that may be classified as hypophyseal chordoma.

From the Neurological Service of the Beth Israel Hospital.

1. Virchow, R.: Untersuchungen ueber die Entwickelung des Schadelgrundes, Berlin, Georg Reimer, 1857.

2. Muller, H.: Ztschr. f. rat. Med. **11**:202, 1858.

3. Ribbert, H.: Centralbl. f. allg. Path. u. path. Anat. **5**:457, 1894.

4. Stewart, M. J., and Morin, J. C.: J. Path. & Bact. **29**:41, 1926.

5. Ribbert, H.: Verhandl. d. Kong. f. inn. Med. **13**:455, 1895.

6. Coenen, H.: Beitr. z. klin. Chir. **133**:1, 1925.

REPORT OF CASE

History.—F. G., a woman, aged 67, was admitted to the hospital on Sept. 3, 1930, complaining of impaired vision in both eyes. The past history was uneventful, except for an operation for "goiter" eleven years previously. The present illness began about six months prior to admission, with blurring of vision in the left eye and vertigo, which were soon followed by diplopia and drooping of the left eyelid. The impairment of vision gradually became worse. One month before admission, vision in the right eye became impaired.

Examination.—The patient was small and undernourished, with generalized atherosclerosis. The blood pressure was 140 systolic and 84 diastolic. The neurologic signs were: pupils unequal, the right being larger than the left, and practically fixed to light, accommodation being incapable of being tested because of the ocular paralysis; complete ophthalmoplegia on the left side, except for slight preservation of downward movement; paralysis of the right external rectus; normal eyegrounds; bitemporal hemianopia; absent knee jerks; diminished achilles jerks, and no pathologic reflexes.

The Wassermann reaction of the blood was reported as doubtful. Roentgen examination of the skull showed erosion and destruction of the sella turcica, with marked encroachment on the sphenoid and the middle fossa. A diagnosis of a basal lesion, neoplastic or syphilitic, in the region of the pituitary fossa was made. In view of the roentgenographic report, a neoplasm was considered more likely. An aneurysm of the circle of Willis was also considered as a diagnostic possibility.

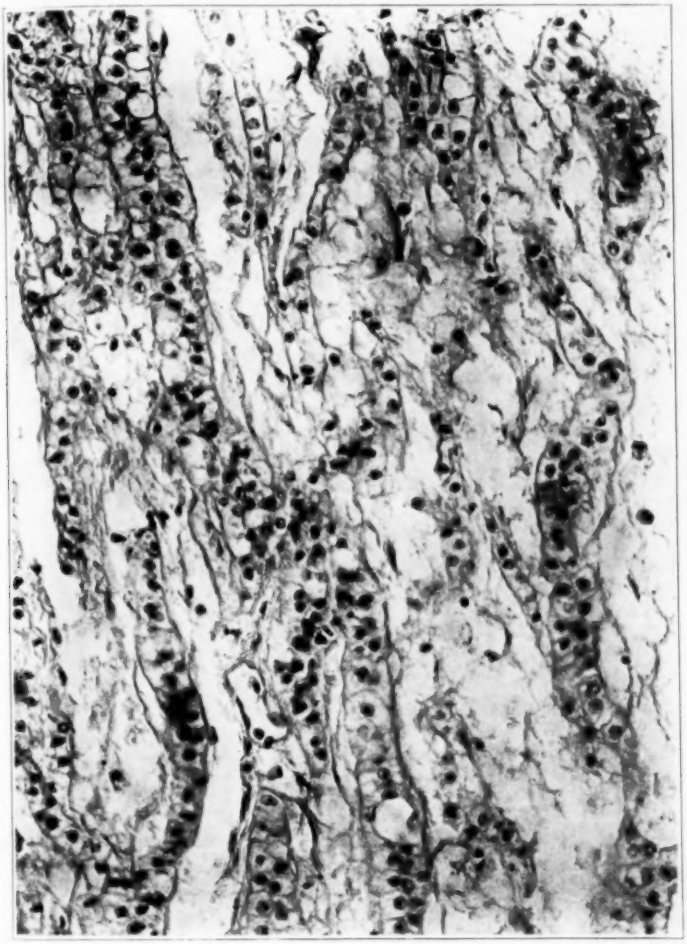
Further serologic studies were somewhat puzzling, positive readings being reported at first without substantiating correlative data at the same time or later. Nevertheless, it was decided to give the patient the benefit of antisyphilitic treatment, despite the feeling of the staff that the process was not syphilitic, as such marked erosion of the sella turcica was known to be very unusual in syphilis. The blood count was within normal limits. Roentgen examination of the chest gave negative results. Examination of the nasopharynx did not reveal any abnormality.

Course.—The patient's vision became progressively worse. Roentgenotherapy was instituted, without demonstrable results. Repeated ophthalmoscopic examination began to reveal a suggestive pallor of the nerve heads, and about the same time it was noted that the patient had become completely amaurotic. She had been strongly opposed at first to surgical intervention, and it was only when she had become blind that she consented to an operation.

Operation.—On October 21, a left transfrontal exploration was performed by Dr. L. M. Davidoff. A smooth-walled mass was found filling the region of the pituitary fossa; its appearance suggested the wall of an aneurysm. The patient's condition became alarming during the operation; after stimulation she seemed to improve. That night she went into a state of collapse and died.

Autopsy.—Gross Examination: A soft, ovoid tumor, the size of a large plum, was situated over the sella and was nonadherent. The surface presented several pea-sized bluish protrusions which, like the mass itself, had a certain similarity to aneurysms. The whole sphenoid bone and the ethmoid bone were very soft, so that one could cut down to the pharynx with a knife. The optic chiasm and tracts were greatly flattened. The circle of Willis was normal. The outer layer of the tumor presented a thin, firm exterior similar to the wall of a sac. Its interior was covered with soft, homogeneous, whitish-gray tumor masses. The base of the brain showed a troughlike depression reaching from the posterior part of the considerably flattened pons to the posterior end of the interfrontal fissure.

Microscopic Examination: The tumor presented the typical picture of a chordoma. The cells were very large, with clear shaggy protoplasm, nowhere showing a homogeneously staining continuous substance. The outlines of the cells were distinct. In only a few spots an orderly arrangement in layers or columns was found. Most of the cells were scattered irregularly, leaving a partly homogeneous, partly fibrillar-appearing substance between them. The nuclei of the cells were



Photomicrograph showing a typical picture of a chordoma, with well outlined, large cells arranged in columns.

mostly large, with a regular distribution of chromatin. Occasionally large nucleoli were found. No mitotic figures were seen. The cells and especially the nuclei had a rather uniform appearance (figure).

The ground substance stained purplish pink with eosin, intensely blue with polychrome methylene blue, metachromatically purplish red with methyl violet and pale pink with van Gieson's stain. It became distinctly red with the microcarmine

stain. A piece of cartilage that was used as a control stained considerably darker and gave a more distinct metachromasia.

The thin-walled sac from the base of the brain was lined with high cylindrical, ciliated epithelium on the outside. This epithelium closely resembled nasal epithelium. The material that was adherent to the inside of the sac was tumor.

COMMENT

In the clinical consideration of this case, the following points stand out prominently: (1) the absence of symptoms or signs indicative of an expanding lesion, which usually are found in cases of intracranial chordoma, and (2) the marked destruction of the sella turcica without the manifestation of any evidence of pituitary dysfunction. The latter phenomenon is in accordance with the experience reflected in the literature, viz., the absence of dyspituitarism in chordomas invading the hypophyseal region. As to the confusing serologic data, one must construe the reports as a probable error, since the histopathologic studies of the brain failed to reveal any alterations indicative of syphilis.

The diagnosis of intracranial chordoma during life can be made only in instances in which tissue for biopsy is accessible. This is possible when the tumor projects into the nasopharynx or when a surgical specimen is removed during craniotomy. It has been suggested that roentgenographic study may give a characteristic picture leading to a correct diagnosis.[7] This seems hardly possible, since the destructive character of any malignant tumor in the vicinity of the sella turcica may simulate such a roentgenographic picture.

The therapeutic aspects of the condition are decidedly disheartening. In my case as in others reported in the literature, roentgenotherapy was of no avail. Surgical extirpation offers only brief palliative relief, as the tumor invariably recurs. The prognosis obviously is bad as to the ultimate outcome, although the slowly invasive character of the tumor would designate it as one of low malignancy. For a further study of the chordomas, the excellent and comprehensive papers by Coenen,[6] and Stewart and Morin[5] are recommended.

7. Bailey, P., and Badgasar, D.: Am. J. Path. **5**:439, 1929.

SUBDURAL CALCIUM DEPOSIT OF THE SPINAL CORD

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The case reported in this communication is that of an extremely heavy calcium deposit in the subdural space of the spinal cord. A search of the literature failed to reveal a record of a similar observation.

REPORT OF CASE

History.—The patient, a white woman, aged 58, was admitted to the City Hospital, on the service of Dr. John McCabe, on May 16, 1927, because of paralysis of the legs, shooting pains and headache. She had always been well until ten years previously. At that time she became acutely ill with dizziness, vomiting, severe headache and backache. The symptoms persisted, with gradual improve-

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ment over a period of six months. For one year she remained well. Then there developed slight spasticity and shooting pains of the legs. The condition gradually progressed, and in three years she became completely helpless and bedridden. For the last two years, voluntary motion of the legs had been completely lost.

Physical Examination.—The results were negative except for the neurologic signs. The pupillary reflexes were normal. Muscular power of the left arm and hand was distinctly weaker than that of the right. The ulnar tendon reflexes were normal, the others diminished. The abdominal reflexes were absent. Voluntary motion of the legs was completely lost. The knee and ankle jerks were absent. The Babinski sign was negative. The skin of the extremities was waxy. Touch, pain and temperature senses were slightly diminished over the abdomen and markedly diminished over the legs. The muscles were distinctly atrophic, especially below the knees. The Wassermann reaction was negative.

The course remained stationary until death on June 9, from lobar pneumonia.

Autopsy.—From the midcervical region to the cauda the cord was completely encased by a heavy chalky deposit, which could be removed in long pencils and completely filled the subdural space. It was not adherent to either the dura or the arachnoid. On chemical analysis it proved to be calcium phosphate. The cord showed an extreme pressure atrophy, which was most marked in the middorsal region. The brain was normal.

Spinal cord showing heavy calcium deposit. In the middorsal region the extreme atrophy of the cord can be seen.

COMMENT

It would seem pertinent at this point to discuss briefly the factors involved in the pathogenesis of this unusual condition. Calcified nodules removed from various parts of the body have an inorganic composition almost identical with that of bone,[1] viz., calcium carbonate 11.2 per cent, calcium phosphate 86.5 per cent and other inorganic constituents 1.2 per cent. These figures are closely approximated whether the sample is a calcified nodule of the thyroid, a calcified thrombus in a blood vessel or a nodule in a tuberculous lung. It is a consequence of the dynamic chemical equilibrium that exists on the one hand between bone and blood and on the other hand between blood and the calcified nodule. The corollary to this theory is that if calcification occurs in a part of the body where interchanges with the blood stream are difficult or indirect, the composition of the calcified mass may vary considerably from the average figures given. For example, a calculus of the urinary bladder may consist of pure calcium phosphate. The formation of calcium deposit found in the case reported was probably very similar to that of calculi or concretions elsewhere, except that in our case, the absence of laminations in the mass suggests a single precipitation. This process differs somewhat from tissue calcification, in which calcium is deposited either in healthy cells, as in the case of bone, or in degenerating or dead cells.

Two other factors favor precipitation of calcium phosphate: (*a*) the presence of an excess of phosphates and (*b*) a low carbon dioxide content. Calcium, phos-

1. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925.

phoric acid and carbon dioxide exist in serum in a delicately balanced equilibrium, aided by the protective action of the plasma colloids.[2] The following formulas represent this graphically:

$$Ca_3(PO_4)_2 + 2\ H_2CO_3 \rightleftarrows 2\ CaHPO_4 + Ca(HCO_3)_2$$
$$2\ CaHPO_4 + Ca(HCO_3)_2 \rightleftarrows 3\ Ca^{++} + 2\ HPO_4^{=} + 2\ HCO_3^{-}$$

Applying the law of mass action, it is evident (1) that an excess of phosphates would favor precipitation of calcium phosphate and (2) that removal of carbon dioxide would operate in the same direction. The very low carbon dioxide content of the spinal fluid introduces factor *b* into our case. There remains but to find a source of increased phosphate.

The patient's past history suggests that ten years before admission she had a purulent meningitis from which she recovered after a stormy course of six months. It is probable that at this time the spinal fluid contained a large number of polymorphonuclear leukocytes, the nuclear protein of which is very rich in phosphates. Disintegration of polymorphonuclear cells incidental to recovery probably liberated a large amount of phosphate in the spinal fluid.

These factors seem to offer a reasonable explanation for the condition found at autopsy.

2. Howland, John: Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1922-1923.

BILATERAL TRIGEMINAL NEURALGIA

A Report of Two Cases; One Relieved by Trichloro-Ethylene

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Trigeminal neuralgia is generally considered a unilateral disease, but a certain number of cases of bilateral pain having been recorded, and its occurrence being sufficiently frequent, the possibility of the development of this form should be thought of in each case of trigeminal neuralgia. The bilateral type most often begins on one side of the face, and after an intervening period of several months or years—more often the latter—the opposite side becomes affected. Accordingly, it is impossible to foretell definitely when symptoms develop on one side only whether or not the patient will suffer involvement on the other side. Hence it is important to attempt first to use trichloro-ethylene in the therapy of this disease; if surgical procedures are to be carried out later, it is imperative to be absolutely certain to conserve the motor root.

To date there have been mentioned in the literature fifty-three cases of bilateral trigeminal neuralgia. Complete histories of only three of these cases have been presented, and for this reason it is deemed advisable to present reports of two new cases, particularly because trichloro-ethylene inhalation has entirely relieved the condition in one of these cases for a period of two years to the time of this writing.

The possibility of bilateral trigeminal neuralgia was first mentioned by Krause. The first complete report of a case of the bilateral disease was that of Winslow.[1] In 1896, he described a case of bilateral trigeminal neuralgia occurring in a man, aged 31. The pain was paroxysmal and involved all three divisions on the left side for a period of four years. At an operation performed at the end of this period,

1. Winslow, Randolph: Ann. Surg. **24**:748, 1896.

the gasserian ganglion was scraped away with a sharp curet. After the operation, the patient had complete loss of sensation on the left side of the face, but was free from pain. Eight months later, the pain returned to involve the right, or opposite, side of the face.

In view of this case, Tiffany [2] in 1896 stated: "The expediency of attempting to save the motor fibres accompanying the third division may be considered. Usually I have not taken the pains to do so, yet I thought that I recognized them. In one of my cases the muscles of mastication were made to contract again and again by passing a tenaculum under the third branch close to the bone. Because of the case reported by Winslow comes the suggestion that perhaps an operation may be expedient on both Gasserian ganglia, and if so, a bilateral paralysis of the muscles of mastication would be unfortunate. While the necessity for a bilateral operation is remote, yet the Hartley-Krause operation will be more complete if the motor root is spared, and I think it can be."

In 1906, Bullock [3] reported a case of bilateral trigeminal neuralgia. Sallie Riley, colored, aged 40, was seen first by him on Feb. 23, 1904. At that time the pain was so terrific that speech was impossible. The pain involved the entire distribution of the right trigeminal nerve and the area of sensory distribution of the inferior maxillary division on the left. The pain had begun in the right side of the face two and one-half years earlier. Following an injection of morphine into the face, the patient was relieved for three months. When the pain returned, it affected the lower jaw of the opposite side and very soon thereafter appeared on the right side. On February 29, under ether anesthesia, the left inferior dental nerve was resected. Four weeks after the first operation, the right gasserian ganglion was removed by the Hartley-Krause technic. Following this, the patient was entirely free from pain. Six months later, uremia developed and the patient died in coma.

Cushing,[4] in 1920, stated that in only 2 of his entire series of 322 patients, or 0.62 per cent, was bilateral neuralgia present. A questionnaire revealed that several other patients had been made apprehensive by twinges of pain on the opposite side, coming on at various intervals, though true tic douloureux never developed on that side.

Frazier,[5] in 1926, reported for the first time a patient on whom the radical sensory operation had been performed on both sides. At this time he stated that in 1,220 cases of major trigeminal neuralgia, only 7 cases, or 0.57 per cent, of bilateral distribution were observed. Because of this, Frazier definitely emphasized the importance of conserving the motor root and the difficulties that may arise if at the first operation the root should be severed. In spite of the fact that he conserved the motor root, the slight trauma at the operation paralyzed the muscles of mastication. It was only trauma that caused the paralysis, because on the seventh day the function of the paralyzed muscles returned.

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2. Tiffany, L. McL.: Intracranial Operations for the Cure of Facial Neuralgia, Ann. Surg. **24**:575, 1896.

3. Bullock, W. O.: A Case of Bilateral Tic Douloureux Treated by Removal of the Right Gasserian Ganglion and Excision of the Left Inferior Dental Nerve, Lancet Clin. **54**:226 (Feb. 25) 1905.

4. Cushing, H.: The Major Trigeminal Neuralgias and Their Surgical Treatment Based on Experiences with 332 Gasserian Operations; Varieties of Facial Neuralgia, Am. J. M. Sc. **160**:157 (Aug.) 1920.

5. Frazier, C. H.: Division of Sensory Root on Both Sides: First Experience in a Series of Four Hundred and Thirty-Two Radical Operations for Major Trigeminal Neuralgia, J. A. M. A. **87**:1730 (Nov. 20) 1926.

Adson,[6] in 1926, reported 13 cases of bilateral trigeminal neuralgia in 839 patients, or 1.5 per cent with bilateral disease. In his series of cases, when the neuralgia was bilateral it generally appeared simultaneously on both sides. However, the paroxysm was rarely equally severe on both sides at the same time—that is, the attacks on one side would subside when the paroyxysm was at its height on the opposite side. In 1 case of bilateral neuralgia, the pain appeared on the opposite side seven years after the initial attack.

Harris,[7] in 1926, mentioned 36 cases of bilateral trigeminal neuralgia, but cautioned against the performing of gasserectomy on both sides owing to the masticatory paralysis that would ensue. It was his opinion that there was less risk of permanent paralysis of the motor root from injection of alcohol into the ganglion than from the gasserian operation, and therefore he believed injection of alcohol into the gasserian ganglion was the proper therapy for bilateral neuralgia.

Dandy,[8] in 1930, mentioned 3 cases of bilateral trigeminal neuralgia. One of these cases had come under his observation a number of years before, when it was not thought justifiable to suggest operative relief, because the motor branches of the trigeminus had been lost in an earlier ganglionectomy when the pain had been unilateral. He operated on the other 2 patients by the cerebellar approach, and they made an uneventful recovery, without any impairment of taste and without any disturbances in the muscles of mastication.

REPORT OF CASES

Case 1.—S. B., a man, aged 78, whose family and past history was essentially unimportant, and in whom physical and neurologic examinations gave negative results, twenty-eight years before had begun to have attacks of sharp pain in the right side of the face. The pain was situated in the lower and upper jaws and involved the second and third divisions of the fifth nerve. The attacks lasted a few seconds and were of extreme severity. The patient was free from pain at varying intervals. The attacks were accentuated by contact and eating, and frequently occurred spontaneously. Nothing relieved the pain.

Five years before, pain appeared on the left side, involving the upper and lower jaws and the supra-orbital region. The attacks were extremely severe and were of knifelike character. The attacks of pain usually lasted for six weeks, and he then was free from pain for six months. Occasionally he had a dull sensation extending over to the right side of the face, primarily in the third division, but not of great severity. The right side of the face felt continually as though an attack were ready to commence.

For the past four weeks, the pain had been so severe that he was unable to eat or to sleep properly. It involved all three divisions on the left side, with only slight twinges on the right. On the second day after I saw him, the periods of intermission increased to such length that he refused therapy.

Case 2.—E. B., a woman, aged 70, complained of pain on both sides of the face. She had had all the teeth extracted and had had three sinus operations. Thirteen years before, she had begun to have pain in the right third division; five years later, there had appeared attacks of acute, lancinating pain in the left second division, while

6. Adson, A. W.: The Diagnosis and Surgical Treatment of Trigeminal Neuralgia, Ann. Otol., Rhin. & Laryng. **35**:601, 1926.

7. Harris, W.: Neuritis and Neuralgia, New York, Oxford University Press, 1926.

8. Dandy, W. E.: An Operation for the Cure of Tic Douloureux, Arch. Surg. **18**:728 (Feb.) 1929.

those in the right occurred only occasionally. For the past eight months, the pain had been most severe in the second and third divisions of the right side, with only occasional twinges in the left second division. For the past month, the attacks had been extremely severe and had occurred from four to five times a day.

After one week of trichloro-ethylene therapy, the pain was completely relieved in both sides, and the patient has been free from pain for two years to date.

COMMENT

In case *2* it will be noted that trichloro-ethylene therapy has entirely relieved a case of bilateral trigeminal neuralgia for two years. Had an operation been carried out for the relief of pain, great discomfort would have ensued from the resulting anesthesia. As far as I am aware, this is the only case of bilateral trigeminal neuralgia alleviated by trichloro-ethylene reported in the literature. It forcibly impresses one with the value of this therapy for the relief of trigeminal pain. As this form of therapy is entirely without harm, it is my belief that it should be employed first in the treatment, but should this fail, surgical measures should then be instituted.

Trichloro-ethylene is a strong, sweet-smelling, white liquid, used in Germany during the Great War for removing grease from the metal parts of machinery and contained in a varnish used to cover the supporting surfaces of airplanes. Plessner, in 1915, presented before the Berlin Medical Society four workers suffering from the chronic effects of acute poisoning, which later was attributed to exposure to trichloro-ethylene. Oppenheim, who was present at the meeting, suggested the use of the drug in the treatment for trigeminal neuralgia. Since then, there have been reported in the literature 197 cases (Glaser [9]) in which this substance was utilized. Though the spectacular results originally reported by Plessner were never obtained by any other observers, it may be safely stated that trichloro-ethylene relieves about 15 per cent of patients suffering with tic douloureux, and eases an equal percentage. Relief from trigeminal neuralgia by trichloro-ethylene is ideal in that the pain is alleviated without resulting anesthesia.

If trichloro-ethylene proves of no avail, a method of temporary relief is found in the injection of alcohol into the second and third divisions, or in combinations of the injection of alcohol with operation. If the first division is involved on one side only, while the opposite side has involvement of the second and third divisions, injection of alcohol into the second and third divisions on one side and resection of the ophthalmic branch on the opposite side may be carried out. As injection of alcohol into the peripheral nerve is only palliative, surgery may be indicated later. Harris [7] has been successful with bilateral injection of alcohol into the ganglion and thinks that this is the procedure of choice. In his experience he has been able to inject alcohol into the ganglion successfully without a secondary infiltration of the motor root.

There are two methods of surgery from which to choose: (1) the subtotal resection of Frazier [5] and Spiller and (*2*) the Dandy [8] partial section of the sensory root at the pons. The Frazier-Spiller method carries with a disadvantage, viz., that the operation must be performed in two stages. The suboccipital operation of Dandy offers a distinct improvement in that the sensory root of the trigeminus can be sectioned and the motor root conserved in a one-stage procedure.

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9. Glaser, M. A.: Treatment of Trigeminal Neuralgia with Trichloro-Ethylene, J. A. M. A. **96**:916 (March 21) 1931; Modern Methods for the Relief of Tic Douloureux, West. J. Surg. **39**:901 (Dec.) 1931.

SUMMARY

1. Bilateral trigeminal neuralgia occurs in approximately 1 per cent of cases, and may appear on both sides simultaneously, as described by Adson, or on one side first and later on the opposite side. The opposite side may become involved as late as twenty-three years after the original attack, as exemplified in my case 1.

2. In one case, trichloro-etheylene has completely relieved bilateral trigeminal neuralgia to the time of writing (two years), without causing facial anesthesia.

3. Of the palliative measures, resection of the ophthalmic division plus subtotal surgical measures, or injections of alcohol in various combinations with operation may be utilized.

4. The major operation of choice in cases of bilateral trigeminal neuralgia is section of the sensory root at the pons by the posterior fossa approach.

Abstracts from Current Literature

THE BLUE ARCS OF THE RETINA. BENJAMIN FRIEDMAN, Arch. Ophth. **6**:663 (Nov.) 1931.

This article discusses a phenomenon first described by Purkinje. If an observer in a dark room, preferably with one eye closed, looks a little to the temporal side of a circle or band of light, he will see, in addition to the source of light, i. e., the primary stimulus, two curved bands of bright blue beginning at the stimulating light and arching across the visual field to the region of the blind spot. At times the enclosed elliptic area is also filled with a faint blue haze. Several subsequent workers, Zeeman, Tscherning and Hubbard, independently reported the same discovery, without being cognizant of Purkinje's original paper because of its inaccessibility.

Hubbard observed that when one fixes his line of sight to the temporal side of the circle, both arcs are present, but when he fixes it to the nasal edge one triangular blue light or blue speck is seen. On the other hand, fixation above showed just the lower arc, while fixation below revealed only the upper of the two. These were apparently different manifestations of the same phenomenon. Amberson, in working on the mapping of visual fields, emphasized that the phenomena cannot be elicited by a stimulus falling in the field that corresponds to the rod-free area, and drew the conclusion that the arcs are rod rather than cone phenomena. Snell, however, suggests a direct relationship between the intensity and the thickness of the arcs and the concentration of the cones; as the recognition of color is a property of the cones exclusively, it speaks for a relationship with the cones.

In an experimental work, Judd attempted to find out whether the rods or the cones are the recipients of the primary stimulus. Using light stimuli of various wavelengths, he determined the least retinal illumination needed to evoke the arcs. His reasoning was that if the rods are the elements that stimulate the activity of the nerves resulting in the blue arcs, the strength of the illumination needed will be higher for wavelengths in the red end of the spectrum than for those in the green, because the rods are relatively insensitive to the longer wavelengths. Experimentally, he showed that there was a definite rise in the illumination values for wavelengths at the red portion of the spectrum, thus indicating an involvement of the rods. In addition, he found certain resemblances between the blue arcs and the Purkinje phase of the after-image, which is conceded to be a reaction of the rods.

It is universally agreed that the arch of the arcs follows the pattern of the nerve fibers between the paramacular region and the disk. This is easily verified by plotting on the tangent screen. Also, the blue spike is inclined from the horizontal as the head is turned to the side. It always follows the inclination of the papillofoveal line. There is much controversy relative to the color of the lights and to the intensity of the arcs as compared with the intensity of the illumination. The statements of dark adaptation on the intensity of the arcs are also conflicting. The author is not inclined to believe that dark adaptation has a weakening effect on the arcs, as has been stated. It is rather definitely proved, however, that the blue arcs depend on the integrity of the retinal elements between the macula and the blind spot. Hence, they cannot be cortical, because they are present only in a healthy eye.

Friedman presents the case of a patient with chorioretinitis and an atrophic patch in the retina lying between the retina and the optic disk. In this the scotoma interrupted the arch of these blue arcs. There is some discussion, in addition, as to the duration of the arcs. Snell found them to be approximately 0.8 second in time.

The mechanism of the phenomena has provoked much discussion. Ladd-Franklin defended the idea of bioluminescence of the stimulated nerve fibers. Judd agreed with this. After-images seem to be of value in arriving at a decision. A rather impressive plea has been made for the theory of secondary electrical stimulation. Beginning with Dubois-Raymond, in 1819, a large number of investigators have demonstrated these currents in the retina by means of a nonpolarizable electrode on the cornea and another on the optic nerve or retina. These currents are distinct from the currents of injury. With the incidence of light, the retina becomes electronegative to the cornea; that is, the current flows outward along the line of sight from the fundus to the cornea. In 1925, Chaffee, Bovie and Hampson, by an intricate and delicate method, found that this current contains a number of summits or maxima, which might be separated into four components, the first two of which they showed to be separate reactions of the rods and cones, bearing out the duplicity theory of von Kries concerning color vision. The curves follow quantitatively the established laws of retinal reaction to light. These findings may be accepted as true indicators of a series of electrical variations in the retina attending its stimulation by light, and it requires no great stretch of the imagination to concede the possibility that these currents secondarily stimulate the retina.

The presence of after-images of these blue arcs has also been discussed. Ladd-Franklin stated that she saw a colored after-image of the blue arcs—a dark olive color. Troland and Snell observed a distinct negative after-image. There is, however, controversy on this question of after-images. Friedman, has been able to see distinctly a colorless after-image. If, as Ladd-Franklin contends, only physical light can produce a chromatic after-image, and mechanical or electrical stimulation cannot do so, then the theory of secondary electrical stimulus for the formation of these blue arcs falls definitely by the wayside. As Ladd-Franklin insists that these blue arcs leave an after-image, the photochemical substance of the retina must be involved. To disintegrate the photochemical substance, one must hypothecate a flow of impulse in a backward direction from ganglion cells to rods or cones; such a backward flow is not inconsistent with experiments on the directional flow of nerve currents. There is a weak link, however, in this conception; it predicates a flow of current during the period of visibility of the arcs at once in a backward direction from ganglion cells to the rods and cones and in a forward direction from the same rods and cones through the same set of ganglion cells toward the cortex.

To summarize the mechanism, then, it is found that a light stimulus of any color, falling on the temporal and the nasal paramacular regions, will produce the arcs and the spike respectively. Since stimulation of the cones alone by the primary stimulus will not evoke the arcs, it is assumed that the initial impulses must be set up in fibers arising from the rods. The electrical discharges or the visible radiation along these fibers affects the underlying retinal elements, either the bipolar cells connected with the rods or cones or possibly both, or else the rod-cone layer directly. If one accepts the theory of an electrical discharge, one assumes a transfer of stimulus from nerve fiber to adjacent cell without benefit of synapse. If one accepts the theory of visible radiation, one admits a condition that has no parallel in nerve tissue. There is too great an unsufficiency of fact and too much contradictory evidence to render judgment in favor of either side at this stage. No one has explained the constancy of the blue color.

The author answers the contention of Snell relative to the necessary involvement of the cones because of the blue color, as follows: For a long time it has been held that the rods also, under proper conditions, are capable of discriminating blue. Helmholtz stated that the lingering blue color of the evening sky and the blue appearance of a snow-covered landscape by moonlight are discerned by the rods after the cones have lost their ability to distinguish color and vision is rendered scotopic. Siven defended this point of view. According to him the dim spectrum is not gray, as ordinarily stated, but is definitely bluish. He referred to the relatively increased visibility of blue at certain times, which is illustrated

by Helmholtz' examples. This is the phenomenon of Purkinje; in decreasing intensities blue is not seen by the macula, but is seen by the periphery. He linked the disturbed recognition of blue with disturbances in the rods. Thus, in poisoning due to santonin he found that the eye was violet blind; therefore, objects appeared in the complementary color — yellowish green (white minus violet). But the central 8 to 10 degrees did not show this anomaly. He believed the visual purple in the rods to be affected, a contention supported by Filehne's investigations on frogs. In patients with icterus, also, yellow vision from the bile salts is well known; since the region of the cones was unaffected, and since, moreover, the visual purple has never been satisfactorily demonstrated in the cones, the assumption is that there is here also a rod disturbance. The significant fact is that night blindness occurs in cases of icterus, and night blindness (rod blindness) is usually accompanied by blue blindness.

The tenet of rod perception of blue is not utterly unreasonable when one considers that in the metamorphosis of color vision the rods were probably the earliest recipients, and the primitive color sensation was probably blue. Observations on insects tend to corroborate this. It is natural to expect the periphery to have been less sensitive to the blue color than the central regions. When the macula was differentiated, the primitive color sense of the rods was pushed into the background, but it may still be demonstrated under the special conditions described. One is now in a position to understand why the blue arcs, if they are solely rod phenomena, appear bluer when the more central fibers are stimulated. It is more difficult, however, to explain why there is such a rapid loss in the intensity of the arcs when the periphery, where the rods are most numerous, is stimulated.

SPAETH, Philadelphia.

DISEASE OF THE SPINAL CORD IN PERNICIOUS ANEMIA. F. W. BREMER, Fortschr. d. Neurol., Psychiat. u. Grenzgeb. **1**:12, 1931.

The more interest is focused on nervous symptoms in pernicious anemia, the more a number of obscurities arise which have not found a satisfactory explanation. It is known that in a large percentage of cases disease of the spinal cord precedes the onset of pernicious anemia; according to MacBride and Carmichael, this is true in 78 per cent of the cases of anemia. Ungley and Suzmann recently found that neurologic signs preceded others in about 75 per cent. If one regards subjective paresthesias as neurologic symptoms, this statement is certainly correct. Statistical reports of this character are not absolute and depend on whether the attitude of the author is neurologic or internistic. The condition of the blood usually brings the patient to the doctor, although the condition may have been present before the abnormal blood picture was in evidence.

Neurologic studies have shown that apparently normal blood pictures are not always proof that one is not dealing with pernicious anemia (Trömmer, Natanson, et al.). Special value has recently been placed on the fact that, with a normal blood picture, changes in the size of the erythrocytes can be established that point to pernicious anemia. Thus Hurst, Waterfield, Warburg and Joergensen, Bremer, and others have published reports of cases of funicular myelitis of the spinal cord in which, in addition to achylia, simple measurement of the red blood corpuscles disclosed a relationship to pernicious anemia. There are unquestionably cases of funicular spinal cord disease that are not due to pernicious anemia. Bremer states that a number of English and American authors maintain that there is no funicular myelitis of the cord without pernicious anemia. He believes that this condition may be associated with a number of diseases, among which pernicious anemia is the most prominent.

There is still a battle of theories regarding the pathogenesis and etiology of pernicious anemia, as well as of funicular myelitis of the cord. The findings of Ucko and Duesberg appeared promising at first. They found changes resulting from saponin poisoning similar to those in funicular disease of the cord. Bremer and Kofler were unable to confirm these findings. Moreover, the cord changes are not "neurotoxic," nor are they specific for pernicious anemia. The fact that

the lesions are associated with the blood vessels, without the vessels themselves being morphologically changed, indicates that one is dealing with "peristatic" processes in the sense of Ricker.

Although little advance has been made in an understanding of the pathogenesis and etiology of funicular myelitis, some progress has recently been made from the clinical standpoint. The disease is often not recognized, and in neurologic circles is sometimes considered a rarity. The diagnosis is often overlooked when the cardinal signs of pernicious anemia are absent. False diagnoses, especially of multiple sclerosis and tabes, are frequent. The clinical picture is most capricious. Symptoms from the posterior and lateral columns are mixed. As Strauss has stated, both symptom groups are mutilated. Two special signs ought to lead to the right track. One can recognize a symptom-duet composed of: (1) Paresthesias, which are present in almost all cases. They occur with a similar intensity only in syringomyelia. Bremer disagrees decidedly that these subjective sensations are a general symptom of anemia (Collier); nor can they be traced only to injury of the peripheral nerves, as was recently stated by Büssow. It is known that changes are also found in the peripheral nervous system (Schäffer and Vialard); but this is not usual. The observations of Bielschowsky, who found a progressive degeneration of the sensory and motor nerve fibers of the tongue, induced Bodechtel and Bremer to undertake a careful histologic investigation of the nerves of the tongue, esophagus and stomach in a case of pernicious anemia with funicular myelitis; the result was negative. The peripheral changes are more accidental accessory manifestations, which are seen also in tabes. Funicular myelitis is chiefly a disease of the central nervous system. (2) Disturbance of deep sensibility; in addition to the paresthesias this deserves especial attention. Even though this portion of the "syndrome of the long root fibers" (Dejerine) is not always definite, and though often enough all qualities are affected, one nevertheless frequently discovers a marked impairment of deep sensibility, which may lead to a suspicion of funicular disease of the cord. A disturbance of the vibratory sense and an often definitely prolonged refractory phase also belong in this category.

Examinations for swellings in the sense of Frey are certainly of great importance, as well as the measurement of chronaxia, which is increased in typical cases (compare with the work of J. Stein). The use of these methods requires experience and judgment; the interpretations have often appeared dubious, especially since the disturbance of attention and the rapid fatigability of patients with pernicious anemia are apt to cloud the picture. Moreover, the theoretical assumption that a pure disorder of the spinocortical system exists does not hold good in all cases. Then, too, the clinical picture and course are variable; spastic pictures can develop as rapidly as tabetic ones; one picture may gradually develop from another, without warranting the formulation of a definite rule.

In unclear neurologic cases, one should never fail to make a fractional examination of the stomach contents; one will thus more often arrive at a correct diagnosis. Achylia is just as little associated with funicular disease of the cord as is pernicious anemia. Hurst considers this combination inevitable; it is interesting, though, what lively opposition his idea encountered (*Brain* **48**:268, 1925). Nevertheless, one will expect to find an achylia in cases of pernicious anemia and will look for achylia especially in the not infrequent cases of "latent" pernicious anemia. In this manner one may often diagnose early cases of funicular myelitis.

Some authors have placed emphasis on accessory psychic manifestations. Bremer has not considered psychic anomalies of such importance, especially in early cases. There is nothing about the mental symptoms that is characteristic of pernicious anemia. The large variety of psychoses with pernicious anemia that have been reported in recent years might lead one to conclude that psychoses are common in this disease. This, however, is not correct. A comparison of the mental disorders in pellagra with those in pernicious anemia is of interest. Pentschew has written a good work on this subject. Pellagra causes many of the symptoms of pernicious anemia; it also displays typical funicular myelitis. Pentschew mentioned angiogenic psychoses and believed that the mental disorder

is caused by a deficiency in the physiologic protective mechanisms of the brain, due to an inferiority of the vascular apparatus of the central nervous system. The question of permeability of the vessels of the brain occupies the center of interest. Reference has already been made to the association between the lesions and the blood vessels, and to the explanation of the manifestations according to Ricker. The permeability of the "blood-spinal fluid barrier" requires attention in pernicious anemia. In a study of twenty cases, Bremer was able to confirm the results of Deutsch and Hauptmann. The quotient of permeability in pernicious anemia, especially in funicular myelitis, is almost always entirely reduced. Of special interest is the fact that in a series of early cases in which the blood picture was still practically normal the quotient of permeability was low.

The development of pernicious anemia may be regarded as disturbances occurring on four parallel tracks: those of the intestinal tract, those of hematopoiesis, those of the nervous system and those of mentation. The development of the disease may stop or be accelerated on any one of these tracks. The blood catastrophe may dominate the picture from the outset—then the nervous and mental disorders recede; it may also be delayed or be entirely absent—then the nervous manifestations dominate the picture. Mental symptoms may be in the foreground from the onset, while the disorder of blood formation and also the funicular symptoms may be the finale.

There is considerable literature concerning liver therapy in pernicious anemia. There are two opposing factions: one does not believe in treatment with liver; the other recommends it warmly, even in funicular myelitis. In some instances remarkable results are described.

The nervous symptoms react differently from the blood to liver therapy. In no case can one speak of a *restitutio ad integrum*. Bremer has never observed a recession of organic symptoms: loss of reflexes or the disorders of sensibility. In early cases the paresthesias may show improvement. With a return of strength, the ataxic phenomena may become less noticeable, and the patient can undoubtedly walk better and with more assurance. Under careful examination, however, the organic neurologic symptoms remain as before. Bremer believes that peripheral disturbances in funicular myelitis are greatly overestimated; they do occur, but are not the rule.

In general, one can say: successful as liver therapy has been in the treatment of the blood disease, it has been of little value in treating the funicular myelitis. In some cases liver therapy has rapidly aggravated the nervous picture. Even Schilling has observed "symptoms of irritation." Taterka and Goldman described states of excitement with liver therapy. Nevertheless, it would seem that systematic liver therapy gradually improves the clinical picture. Mason saw improvement only after four years of continuous liver therapy. The progress of the disease may even be retarded by such treatment. There is much in the idea that result can be expected only with prolonged and adequate liver therapy. This form of treatment is the only available weapon, and it would be a mistake to discard it on account of theoretical considerations and disappointed expectations.

BOLTZ, Binghamton, N. Y.

NEUROLOGIC SYMPTOMATOLOGY OF SUBTENTORIAL TUMORS. G. AYALA, Riv. oto-neuro-oftal. **8**:424 (Sept.) 1931.

In his discussion of subtentorial tumors before the First International Neurological Congress, Ayala draws on thirty-four cases that he has observed and a large number of reports collected from the literature. Fundamentally, he says, the distinctive regional characters of the clinical picture presented by these tumors may be grouped under two headings: (1) the disturbances in muscle tone, and (2) the disturbances in the intracranial circulation. He calls attention to the marked tolerance and adaptability of the brain stem and cerebellum to the compressing and infiltrating effects of these tumors and the fluctuation in symptoms

that this brings about. Moreover, he says: "No one symptom, general, vestibular or pontomedullary, taken alone, can be considered pathognomonic of subtentorial tumors."

While the fully developed clinical picture of a subtentorial tumor is almost unmistakable, the neurologist should be on the lookout for the earliest signs, which, Ayala says, consist in some discomfort and stiffness of the neck, with difficulty in movement and paroxysmal headaches with no peculiar characteristics, which are generally attributed to indigestion or fatigue. Even at this stage, incipient papilledema may be found, without reduction in vision or narrowing of the visual fields. Paresthesias in the face and tinnitus often precede disturbances in corneal sensibility, vertigo, deafness and other phenomena of paralysis or compression. Sudden reduction in vision, with equally sudden clearing up, may be seen. Patients may complain very early of slight uncertainty in walking and of nausea with vomiting on sudden movements of the head, as in getting up in the morning, and these pseudodigestive phenomena are sometimes the cause for appendectomy.

From the clinical standpoint, the author divides tumors of the posterior fossa into four main groups as follows:

Group 1: Tumors of the brain stem itself make up about 10 per cent of subtentorial tumors. Their location is recognized by the interference with the centers and conduction tracts in the brain stem itself, such as hemiparesis, hemihypesthesia, paralysis of the palate and tongue, disturbances in respiration, polyuria, glycosuria, etc., and especially the crossed paralysis, skew deviations and paralysis of associated lateral movements of the eyes.

Group 2: This group is made up of tumors growing from the meninges and from the nerves at the base, and their symptomatology is especially neural in type. Paracusia, followed by slowly advancing deafness, is one of the earliest signs of an acoustic tumor; these tumors may be bilateral although in some cases a single tumor may cause bilateral deafness. These patients often experience uncertainty in standing and walking, frequently in the form of attacks, and they usually show nystagmus, which is usually horizontal with the rapid component toward the side of the tumor. Along with this is a tendency to deviation toward the side of the tumor when the eyes are closed and inexcitability of the vestibule on the same side with central deafness, sometimes associated with hypo-excitability of the opposite vertical canals with preservation of the activity of the opposite horizontal canal. This formula, however, is not absolute. Neighborhood signs are not uncommonly present. Paresthesia and hypesthesia in the face, loss of the corneal reflex and sometimes slight weakness in the facial musculature on the same side are occasionally seen. General signs, such as papilledema, headaches, suboccipital tenderness and inclination of the head toward the affected side with rotation of the chin in the opposite direction, may be found.

Group 3: This group consists mostly of tumors of the cerebellar hemisphere. The headache in such cases may begin violently but usually insidiously, with heaviness and fulness in the head and stiffness in the neck. Pain may be produced by passive movement of the head in various directions and the patient himself may mention the occurrence of such phenomena on spontaneously moving the head. Moreover, the head may assume a position, which varies from case to case, in which the headache is relieved. Ayala calls attention particularly in these cases to the disproportion between the signs of intracranial hypertension and the psychic disturbances. These patients "do not lose the consciousness of the seriousness of their disease." This is usually in rather marked contrast to the condition observed in hemispheric tumors. These patients may suffer paroxysms of visceral pain or even urogenital disturbances. Pyramidal signs and paralysis of cranial nerves are usually late phenomena, but there is no definite symptomatology that will distinguish an intracerebellar from an extracerebellar tumor. The physical signs are often misleading, and it is quite frequently impossible to tell which cerebellar hemisphere is affected. The lowering of vestibular excitability is often a prominent feature, and disturbances in gait are usually of great significance. The charac-

teristic signs of cerebellar disease—disturbances in tone, coordination, etc.—are more frequent in diseases of the cerebellar hemisphere. A tendency to fall forward or backward is not particularly diagnostic.

Group 4: The symptomatology in this group is usually due to midline tumors, often projecting into the fourth ventricle. The course is usually stormy, with violent onset of headaches, choked disks and bulbar crises that may in attenuated form give rise to visceral symptoms such as angina, dysuria, meteorism, and disturbances in cardiac rhythm, blood pressure and respiration. Tonic attacks, extreme vertigo, cerebellar fits and decerebrate rigidity may be seen in this type. Such tumors, owing to their production of intracranial hypertension, are most apt to give rise to psychic symptomatology.

FREEMAN, Washington, D. C.

THE DORSAL LONGITUDINAL BUNDLE OF SCHÜTZ—FASCICULUS PERIEPENDYMALIS—AND ITS RELATIONS TO THE CENTRAL GRAY MATTER. OTTO MARBURG, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:135, 1931.

According to Marburg, the bundle of Schütz represents a long fiber system which runs throughout its entire course in close proximity to the ependyma. In order not to confuse this system with the posterior longitudinal bundle, which is also designated by some authors as the dorsal longitudinal bundle, Cajal has suggested that the tract under discussion be designated fasciculus periependymalis. It consists of fibers that are partly centrifugal and partly centripetal, and is probably in relation with the tuber nuclei in the thalamus, which are situated somewhat oral to the corpus mamillare; at least this is the case when one studies sagittal sections of this tract in man. It is impossible to determine whether one is dealing here with the ansa ganglion or with the nucleus mamillo-infundibularis; the fact that the fibers are situated more mesially would favor the latter localization. There is, however, no doubt as to its relationship with the mesial nuclei of the thalamus (nuclei paraventricularis); it is here that it is difficult to decide whether one is dealing with afferent or with efferent fibers, or with both.

The pontomesencephalic portion of this system can be distinguished much more readily. There is no question that the fibers originating in this region are efferent, even though the presence of afferent fibers cannot be absolutely excluded. The nuclei in relation to the tract here are those of the annulus aqueductus: nucleus medianus, paramedianus and lateralis, and the nucleus parvicellularis annuli aqueductus, to which the ganglion dorsale tegmenti of Gudden is attached most caudally. In the tract one can make out distinctly the fibers coming from the nucleus paramedianus and parvicellularis, and also perhaps from the ganglion dorsale tegmenti of Gudden, i. e., from the nuclei into which "olfactory fibers" enter; these "olfactory fibers" reach the nuclei by way of the fasciculus interpedunculotegmentalis and of Wallenberg's fibers from the basal olfactory bundle.

Careful examination of the mesencephalic nuclei reveals a certain analogy to the nuclei of the medulla oblongata. In the latter there are also found closely situated nuclei that are composed of small and moderately sized ganglion cells; these are: nucleus triangularis, nucleus intercalatus, nucleus prepositus and nucleus rollerii. It is with these nuclei that the third portion of the fasciculus periependymalis, the portion belonging to the medulla oblongata, is also in close relation. In this connection it must be remembered that the nucleus intercalatus contains cells that are probably very similar to, if not identical with, the cells of the nucleus triangularis.

Whereas it is generally accepted that the mesencephalic portion is predominatingly influenced by the olfactory system, there is also abundant evidence now at hand that the medullary portion receives predominatingly vestibular, gustatory (by way of the nucleus glossopharyngeus and intermedius), vagal and trigeminal impulses, although the various connections between these systems and the various nuclei have not as yet been definitely determined.

If one could assume that the small cells are relay stations for centripetal impulses or for direct reflex arcs, and that the large cells subserve motor func-

tions, one could also assume that the large cells of the nucleus prepositus, intercalatus and rollerii, analogously to the ganglion tegmenti dorsale, are also motor elements the fibers of which, however, do not go directly to effector organs but act as coordination mechanisms, similar to Kohnstamm's coordination nuclei, for the system under discussion. In the same sense one may also look on the small cells as sensory elements which are, on the one hand, associated reflexly with the so-called coordination nuclei, and, on the other hand, as Spitzer has pointed out, as sensory stations that receive centripetal impulses for hunger, appetite and disgust, whence they are further conveyed to consciousness. It must, however, be admitted here that it still remains questionable whether these impulses ascend by way of the fasciculus periependymalis; nor is the function of the fibers of the pontomesencephalic portion, running with the posterior longitudinal bundle, understood. Still, it is difficult to believe that the close proximity of these fibers to the aforementioned nuclei is a mere coincidence.

In collaboration with Takagi, Marburg long ago pointed out that these tracts are especially well developed in ruminants, and that the mechanism for vomiting might perhaps be set into operation through these systems—a view also expressed by Winkler. According to Marburg, vomiting may be said to resemble the antiperistaltic movements observed in ruminants; it may be brought about reflexly without the intervention of consciousness, even though it may also occur consciously by disgust. In the latter case, olfactory as well as optic and gustatory factors may play an important rôle in the act of vomiting. On the other hand, it is well known that vomiting may also occur reflexly through sensory irritation of the pharynx. Bearing all these facts in mind, it would seem that all these mechanisms have their centrifugal pathway in the fasciculus periependymalis, and that vomiting may occur when any part of this system is affected. The practical importance of this system is that whenever vomiting occurs in cases of tumor of the brain the vagus nucleus need not necessarily be affected directly, as in posterior fossa tumors, but that vomiting may occur also in lesions lying orad in the midline of the brain (sylvian aqueduct). In such localizations the vomiting need not necessarily be attributed to increased intracranial pressure, because it may be due to disturbances in the periependymal system. From this entire discussion it is obvious that whatever other functions this system may have, it is certainly a very important vegetative system.

KESCHNER, New York.

EXOPHTHALMOS IN INFANTILE SCURVY. JOHN HUGHES DUNNINGTON, Arch. Ophth. **6**:731 (Nov.) 1931.

This article is a discussion of the type of infantile scurvy that is not often seen, namely, infantile scurvy with exophthalmos. The author first discusses infantile scurvy from the standpoint of its early history. It is of interest that although scurvy has been known for many years, for, as the author states, "the reference of Hippocrates to the large number of men in the army who suffered from pains in the legs, and gangrene of the gums, which was accompanied by loss of teeth, seems sufficiently definite to be identified as this disease," it is difficult to establish with any certainty its earliest description. Its occurrence in infants was first recorded by Glisson in 1668, but it was not until 1862 that there was any mention of exophthalmos as a complication. The report of the American Pediatric Society in 1898 was based on 379 cases of infantile scurvy. Forty instances of swelling and protrusion of the eyes were reported, i. e., approximately 10 per cent. The author thinks that this is an erroneous percentage, and that it should be considerably less. He bases this statement on the fact that there are only twenty-two detailed case reports in the literature of exophthalmos with scurvy. The author's historical section is most detailed and interesting.

According to the investigations of Aschoff and Koch, Hess and others, scurvy is considered as a pathologic condition of the endothelial cells of the blood vessels produced by a lack of vitamin C in the food. Thus an increase in the permeability

of the blood vessel walls is important as a factor in the production of hemorrhage. The hemorrhages that occur between the orbital plate of the frontal bone and the subjacent periosteum are apparently the cause of the exophthalmos. Other cases were reported, as the author quotes, of a hematoma of subperiosteal origin. There were no cases reported in which only the floor of the orbit was involved. This is apparently the reason why the displacement is always forward, downward and outward; the subperiosteal hemorrhages are always above and on the medial wall of the orbit. The hemorrhagic origin of the exophthalmos is discussed from the standpoint of work done by Hart and Lessing, and Harden and Zilva, on experimental scurvy in monkeys. Barlow, Steindorff and others reported cases of subconjunctival hemorrhage, Kaltz one of hemorrhage into the anterior chamber and Hirschberg one of retinal hemorrhages as an accompaniment of an orbital hemorrhage.

The varying severity of the exophthalmos is striking. Every conceivable degree of bulging has been noted, from the slightest swelling to the most marked exophthalmos. Those recorded as slight protrusions are open to criticism, for it is evident that such a diagnosis is difficult either to make or to dispute. As edema of the eyelids is frequent in the subacute or latent type of infantile scurvy, it is possible that some of the so-called mild proptoses were of this nature. The exophthalmos may be sufficiently pronounced to endanger the cornea. A large corneal erosion complicating extreme exophthalmos led Jost to puncture the orbit and do a total tarsorrhaphy rather than wait for the effects of antiscorbutic treatment; the result justified the procedure, while conservative measures in a similar case reported by Tallei resulted in a dense corneal leukoma. Van der Straeten reported corneal ulceration with perforation as a complication in an extreme case. If the hemorrhage is confined entirely within the orbit, the exophthalmos is not accompanied by any involvement of the lids (Buys, Blake). In most of the cases, however, the blood oozes in from the orbital septum, producing ecchymosis of the lids, particularly the upper lids. The swelling of the lid may become so tremendous as to mask the actual protrusion of the globe. The exophthalmos usually precedes the involvement of the lids, or the two occur at the same time.

The exophthalmos is nonpulsatile and irreducible; any attempt at reduction causes great pain. Such manipulation may precipitate a hemorrhage into the lid or cause an increase in the proptosis. The proptosis may involve one eye or both; usually, if it is bilateral, one eye is affected before the other. In confirmation of Still's statement that the left eye is involved more frequently than the right, the author's analysis of 17 unilateral cases showed the left eye to be affected 11 times while the right eye was involved in only 6 instances. Most writers have stated that the motility of the eye is not impaired, but Jost found the eye to be immobile in his most extreme cases. It seems as if the impairment of motility should be in direct proportion to the severity of the exophthalmos. The occurrence of impaired motility is usually a late manifestation of scurvy; however, Barlow and Schlesinger have recorded its presence as the initial sign of this disease. Diagnostic methods have improved so markedly during the last twenty-five years that it is highly improbable that any one will ever be forced to make a diagnosis of scurvy on the presence of exophthalmos alone. It is important, however, to bear in mind that this complication may arise before the classic symptoms are present.

The author reports in detail the case of a white child, aged 7 months. The recovery was satisfactory and seemed to depend almost wholly on the administration of 3 fluidounces (89 cc.) of orange juice daily. The author's summary is: "Infantile scurvy is not an infrequent cause of exophthalmos in children less than 2 years old. The direction of the proptosed eye is uniformly forward, downward and outward. The sudden onset of the condition is characteristic, and its haemorrhagic origin is undisputed. The diagnosis is easily made, and rapid and complete recovery follows antiscorbutic treatment."

SPAETH, Philadelphia.

SQUAMOUS CELL EPITHELIOMAS OF THE HYPOPHYSIS. GINO PATRASSI, Riv. di pat. nerv. **38**:483 (Sept.-Oct.) 1931.

The author describes a case of epithelioma of the hypophysis and reviews this important subject. He begins with the embryologic data concerning the development of the pituitary gland from an extroflexion of the ectoderm of the mouth which soon assumes the form of a pouch (Rathke pouch). At the sixth week of embryonal life, a process of pedunculation originates, and the hypophysis is formed. At the tenth week of embryologic life, the canal is solidified and a process of interruption follows which its inferior half contributes to the formation of the pharyngeal hypophysis, consisting of poorly differentiated hypophyseal tissue and a larger portion of squamous epithelium. The upper portion of the duct remains included in the cranial cavity, and the residuals are later identified under the aspect of squamous epithelial nests. Civalleri and Haberfield demonstrated how accumulations of cells are even detectable in the thickness of the sphenoid bone. Luschke, Saxer, Caselli and Erdheim called attention to the existence of a group of squamous epithelial cells in the pituitary gland itself. Erdheim, in twenty hypophyses studied in serial section, found epithelial nests in ten. In embryos and in new-born subjects Erdheim did not find cellular accumulation, thus concluding that in the early stages of life extent of this accumulation is so small as to escape attention and that the progressive increase in volume makes it visible in later periods of development. The epithelial nests consist generally of simple basal cells and occasionally of a spinous layer of cells. No keratohyaline or other epidermoidal formations are found.

The tumors that develop from the remnants of these epithelial cells are also known as Erdheim tumors and may correspond to two fundamental types, the cystic and the solid type, which are generally combined in more or less various proportions. The cystic form is the more frequent, and the wall of the cyst discloses papillary formations which give to the tumor a cauliflower appearance. The tumor mass may undergo calcification and transformation into bone. The tumor mass may be suprasellar or intrasellar, according to its origin from the epithelial nests located over the anterior portion of the pituitary gland or from those located in the sphenoid bone itself.

The author then takes into consideration the modifications of the sella following development of the tumor mass and discusses the symptomatology referable to the infundibular region, pointing out that it is not rare to find that the pituitary gland in these cases appears more or less intact.

Histologically, the tumor is characterized by a stratified squamous epithelium which may be more or less thick in the various areas of the tumor. The author asserts that the external layer is represented by a series of cuboid or cylindric elements, occasionally assuming a palisade disposition. Next follows a layer of roundish polyhedral cells and finally layers of squamous cells, which tend to become concentrically stratified. Some authors have compared the histologic features with the epidermis or the epithelium of the mouth. Occasionally, the squamous epithelial appearance becomes poorly recognizable because of the degenerative changes that develop. Occasionally, only a layer of cylindric cells may be recognizable.

The author then discusses the possibility of keratinization of the epithelium and quotes Erdheim that in tumors of the pituitary duct neither keratohyalin nor a process of cornification is ever encountered. This is in contradiction with the statements of other authors that pearl-like formations, granules of keratohyalin and even true keratin occur. The author thinks that parakeratosis finally takes place in these tumors based on physicochemical changes of the degenerated epithelium. He concludes that the presence of cornification or parakeratosis is not incompatible with the oropharyngeal origin of the neoplastic tissue and therefore with the diagnosis of tumor of the hypophyseal duct. Hydropic metamorphosis of the epithelial cells is frequent, and this phenomenon of liquefaction combined with the palisade aspect of the cells of the basal layer constitutes the most important analogy between the adamantinomas and the tumors of the hypophyseal duct.

The stroma of the tumor is formed by vascular connective tissue and by neuroglia or nerve tissue whenever the tumor invades the brain substance. From the liquefaction of the stroma pseudocysts may originate. Degenerative phenomena leading to calcification and ossification may take place in the supporting connective tissue. Reactive inflammatory phenomena may also be present.

As to whether the growth is benign or malignant, the author thinks that there are cases with a benign course notwithstanding the histologic carcinomatous structure. As for differential diagnosis, the distinction between the Erdheim tumor and a cholesteatoma is at times difficult, though cholesteatomas have more tendency toward keratin formation and less tendency toward liquefaction. The extraventricular seat of the tumor speaks against an ependymal or choroidal genesis. More easy is a differentiation from cysts of Rathke's pouch, which are generally found in the thickness of the sphenoid bone. The differential diagnosis from meningiomas is easy.

FERRARO, New York.

PERIMENINGITIS. EUGEN POLLAK, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:297, 1931.

According to Pollak, perimeningitis, epimeningitis or acute external spinal pachymeningitis, is not rare. It seems to affect males two and a half times as frequently as females. Of 41 cases studied by Schmalz (cited by Pollak), about 70 per cent occurred during the first half of life. The condition is usually secondary to a primary septic process, which may be in the nature of a furuncle, phlegmon, whitlow, osteomyelitis, decubitus, empyema or polyserositis. It has also been observed after acute infectious diseases (pertussis and pneumonia). The characteristic symptoms of the disease are: general hyperesthesia, especially of the lower limbs, abdominal oversensibility, paresthesias, severe generalized pain, fever and leukocytosis from the primary septic disease. The cerebrospinal fluid, as is to be expected, is clear and shows neither pleocytosis nor increased albumin. A negative spinal fluid is characteristic of perimeningitis, regardless of whether or not there is a coexisting involvement of the spinal cord. In doubtful cases the correct diagnosis can be established by the finding of pus in the epidural space on introduction of the spinal puncture needle into it without the dura itself being penetrated. In order to obtain the best therapeutic results, it is imperative to remove the pus from the epidural space before the appearance of symptoms in the spinal cord.

After these preliminary remarks, Pollak gives a detailed clinical report of a typical case of perimeningitis in a woman, aged 24. The perimeningitic process was secondary to a furuncle and manifested itself by an extradural collection of pus in the spinal canal from the thoracic vertebrae down. At necropsy there were also found symmetrically situated paravertebral abscesses at the level of the third and fourth thoracic vertebrae. The leptomeninges were intact, and the subarachnoid space showed no evidences of inflammation.

Histologic examination revealed a myelopathy that was definitely due to circulatory disturbances in the spinal arteries. The pathologic process consisted of malacia of the central portion of the cord and of the ventral portion of the dorsal columns, with typical marginal involvement. It is noteworthy that there were no evidences of hemorrhage or of inflammation in the cord, meninges or vessels. Most of the cells in the areas of softening were gitter cells, derived principally from the glia tissue. Generally speaking, the glial hyperplasia was less marked than one would expect from the severity and extent of the parenchymatous destruction. The reparative functions of the supportive tissues were apparently remarkably diminished. It was this that was most likely the cause of the extensive cavity-like formations, which differed from ordinary softenings of parenchymatous tissue.

The pia disclosed a peculiar type of swelling, characterized by an unusual succulence of the connective tissue processes, which gave that membrane a thickened appearance. Here, too, no infiltrations were observed. The reaction of the

leptomeninges was of the type usually observed in severe degenerative intraspinal processes, i. e., slight proliferation of the connective tissue elements in the form of collections of macrophages and of fat granular cells. The dura mater showed no noteworthy changes other than a slight swelling resembling that in the leptomeninges. There were no evidences of external pachymeningitis.

Pollak comments on the difficulty encountered in an attempt to explain a malacia of the cord confined to a definite level supplied by blood vessels, without pathologic changes in them or in the meninges. The malacia was focal, with areas in which there seemed to be a confluence of several smaller foci leading to a large softening. The softenings at the margin of the cord were total and could not be distinguished from the typical vascular necroses of the myelopathies, regardless of whether the cause of the vascular disease is compression, syphilis, tuberculous or other infections or trauma. As there were no evidences of the presence of any of these etiologic factors to account for the malacia, Pollak believes that it was due to chemicophysical disturbances of the nerve elements in consequence of circulatory disturbances, which may have been the cause or the sequela of a change in the parenchyma. He therefore attributes the disease of the cord to circulatory interference, which was due not to organic changes in the blood vessels but to an irreparable and prolonged functional disturbance of the blood vessels in the nature of a vasomotor paralysis. He believes that one of the functions of the dura and the other meninges is to carry away abnormal accumulations of fluid from the cord through the channels and clefts within these membranes. He assumes that in the case under discussion the septic epipachymeningeal process led to an injury of the vasomotor apparatus of the vessels that supply the cord, on which was superadded the inability of the meninges to carry off the pathologically excessive water content from the parenchyma of the cord, which ultimately led to its destruction and consequent softening.

KESCHNER, New York.

FUNDAMENTAL OUTLINE OF TRAUMATOLOGY OF THE CENTRAL NERVOUS SYSTEM. O. ROSSI, Riv. di pat. nerv. **38**:797 (Nov.-Dec.) 1931.

The author gives a comprehensive review of traumas of the central nervous system and adds facts derived from a wide experience. One of his most important contributions is the description of a syndrome, which may be called the "Rossi syndrome," due to rupture of intrapial blood vessels. In this syndrome, which was first described in 1921, the trauma leaves the bony structures of the skull intact and is not followed immediately by neurologic symptoms; the latter may appear sometimes more than twenty-four hours after the trauma. The author separates this syndrome of rupture of intrapial blood vessels from that of subarachnoid hemorrhage. Among the most important differential characteristics is the fact that the focal symptoms in the "Rossi syndrome" are clear and develop rapidly. Another important element is the topographic relationship existing between the seat of the vascular lesion and the focal symptoms. The syndrome is essentially cortical and usually leads to an incomplete recovery of function.

The author then discusses the so-called indirect lesions from trauma of the central nervous system, lesions that are not the result of direct contact between the traumatizing agent and the nerve tissue. In this type of lesion the bones are generally respected. Rossi divides indirect lesions into those that follow immediately after the trauma and those that are delayed in their appearance. Among the former he describes lesions of vascular origin and lesions of parenchymal nature. Lesions of vascular origin include: (*a*) hematorachis, (*b*) hematomyelia and (*c*) capillary apoplexy. Lesions of the nerve parenchyma include: (*a*) the formation of small cavities that may or may not surround the blood vessels, and (*b*) the formation of areas of necrobiosis, among which are crushing (*Quetschung* of German authors) and laceration (*Zerrung*). Rossi also describes structural changes in the axis cylinders, in the nerve cells and in the glial elements.

Among the delayed indirect lesions Rossi describes: (1) meningopathy (productive meningopathy and circumscribed serous meningitis); (2) arteriopathy (delayed apoplexy and thrombosis); (3) structural modification of the nerve elements.

Rossi emphasizes the occurrence of hematomyelia following trauma, but does not seem to favor the individuality of traumatic hematorachis. In regard to the capillary apoplexies, he emphasizes the importance of small minute hemorrhages in generating islands of gliosis or definite permanent modifications of blood vessel walls, facts that might be very important in interpreting some symptoms occurring in the so-called traumatic neuroses.

Speaking of the reaction of the meninges, the author seems to confirm Marburg's finding of a traumatic meningopathy consisting in a thickening of the meningeal tissue. He also admits the existence of thickening in the pia mater. Describing the lesions in the blood vessel walls, Rossi has never found the so-called "traumatic endarteriopathy" of Marburg in which the intima undergoes hyperplastic changes, whereas he describes a process of connectivation with loosening of the blood vessel walls, a process which he divides into three subcategories: (1) metamorphic arteriopathy, (2) productive arteriopathy and (3) neoforming arteriopathy. Lesions are very scarcely found in the veins, whereas in the capillaries Rossi describes two distinct processes, one consisting in the considerable diminution of argentophile reticulum surrounding the capillaries and the other in a phenomenon of metaplasia of the reticular tissue into collagen tissue.

Concerning the pathogenesis of the lesions in trauma of the nervous system, Rossi claims that some of the lesions that immediately follow the trauma, as for instance rupture of the pial blood vessels, hematomyelia, rupture of the axis cylinders, displacement of the nucleus and nucleolus in the nerve cells, the formation of primary cavities, the deformation of the central canal of the spinal cord and small areas of crushing and laceration, all may be directly correlated with a mechanical factor, whereas the primary destruction of the nerve tissue, especially in correspondence with the posterior columns, needs another explanation. Ricker's theory of a paralysis of the vasoconstrictors can explain only part of the situation; another part of the explanation resides probably in the changes in the reticular fibers of the capillaries, the function of which may be not merely mechanical but also biochemical. The lesions detected at a later time after the trauma may in part be explained on the basis of the arteriopathy and meningopathy, and on the basis of toxic changes originating from the formation of autoneurotoxins.

Finally, the author takes into consideration the existence of true concussional syndromes corresponding to the functional ones, which he divides into one syndrome that he proposes to name "traumatic shock" and two other syndromes, one represented by "spinal stupor" (Rossi) and the other by "abortive cervical concussion."

The article reports a fundamental and important piece of work which is of value in connection with medicolegal questions.

FERRARO, New York.

A CASE OF ANGIORETICULOMA AND THE PATHOLOGY OF HEMANGIOMA. MASAMICHI TOYAMA, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:248, 1931.

Toyama reports in detail a case of hemangioma characteristically localized in the cerebellomedullary angle. It is noteworthy that the patient had had a cerebellar cyst for which he was operated on successfully ten years before the appearance of symptoms of a tumor in the cerebellomedullary recess, for which he was again subjected to an operation. Following the second operation, an air embolus developed from which the patient died. The second tumor is the subject of the present communication.

Microscopic examination revealed that the tumor was attached caudally to the medulla, which it invaded so that the dural portion of the latter was spared, whereas its ventral portion was compressed caudad to the olive. Some parts of the tumor also seemed to have invaded somewhat the cerebellum. Even on macroscopic examination it was evident that the tumor was unusually rich in

blood vessels; its caudal portion contained large spaces full of blood, whereas its oral portion also showed similar hemorrhagic spaces, though they were much smaller. The center of the tumor mass consisted of a large cystic cavity.

Histologically, the tumor was a typical angioma, corresponding completely to the type of tumor described by Roussy and Oberling as angioreticuloma, or reticulo-endothelioma. The cells of the tumor were typical endothelial cells. Stained with fat stains, they were found to be devoid of lecithinoid substances, so characteristic of Niemann-Pick's disease and of amaurotic idiocy, but contained fat resembling that derived from broken-down myelin. As, however, the case showed no evidence of destruction of myelin, it is difficult to attribute the accumulation of fat in the cells to this source. Besides this, there were also observed considerable numbers of cells that contained no fat at all. Large portions of the tumor mass also contained cells which, although laden with fat, still retained their cellular character. It is also noteworthy that many fat-containing cells, which had grown to an unusually large size, contained nuclei that showed distinct evidences of a degenerative process; these cellular masses stood out in the sections as large, homogeneous, poorly stained islets that could not be distinguished from the surrounding tumor tissue. Owing to the combination of fatty degeneration and infiltration in these cells, Toyama was unable to determine the source of the fat.

The author was also unable to determine the origin of the tumor cells. On superficial examination it appeared that the arachnoid might have been the source of the tumor formation, but a detailed examination of the pia-arachnoid showed that this was not the case. The tumor certainly did not have the appearance of a meningioma of the type described by Beeno Schmidt, Mallory, and Cushing and Bailey. Its structure also differed greatly from that of the tumors designated by older writers as angio-endotheliomas. There is no doubt that the growth was not a variety of blastomatous tissue, but a fully developed tissue—an angioreticuloma. It is also noteworthy that the tumor contained areas that conformed to simple cavernomas and could be regarded as angiogliomas; these areas, however, could be definitely seen to have undergone, for some reason or other, changes that differed from those of the other cells. Disregarding the cavernous spaces in the tumor, the cystic formation within it was the result of a process of fusion of the type ordinarily observed in gliomas, which is produced by the fusion of several smaller cysts into one large cystic mass the walls of which consist not of glia but of fibrous connective tissue. In the case under discussion the inner wall of the cyst was not lined by endothelial cells, and although the cyst was to a great extent in the center of the tumor, there is no doubt that the latter did not originate from the cyst wall.

From this entire study Toyama concludes that the new growth in this case was a solitary tumor that could be homologized with the neurinomas, and that it represented some defect in the "anlage" of the vascular system which, as has been shown by Linden, may find expression in some cases in a single localization and in other cases in several localizations.

KESCHNER, New York.

CYTOLOGIC STUDIES OF RETINA. MILTON L. BERLINER, Arch. Ophth. **6**:740 (Nov.) 1931.

In the optic nerve, as in the central nervous system, three types of neuroglia occur, namely, the astrocytes, the microglia and the oligodendroglia. The astroglia, with its two types, protoplasmic and fibrous, is found throughout the nervous system. This type of neuroglia is characterized by the fact that the cells have some prolongations, the ends of which are applied against the walls of the small vessels. The microglia, in all probability of mesodermic origin, are phagocytic and correspond to the histiocytes of the connective tissue system. The oligodendroglia are seen in rows, and are especially conspicuous in the white matter, where their prolongations envelop the nerve fibers. In the retina of man, where normally there is no myelinization, there are no oligodendroglia formed;

the only glia cells that appear are the astrocytes and the microglia. The intervention of the latter in several pathologic processes of the human eye has been described by Lopez Enriquez.

In order to determine whether the presence of medullated nerve fibers is constantly correlated with the existence of oligodendroglia, it seemed advisable to study the retina of the rabbit, an animal in which myelinated fibers are normally found. Also, since these myelinated nerve fibers occur in a more or less restricted area in the retina of this animal, it allows the possibility of comparison with other areas of the same retina in which there is no myelinization.

The technic followed for the demonstration of the characteristics of the oligodendroglia in the retina of the rabbit was the silver carbonate method of del Rio Hortega. The study demonstrated that the presence of myelinated fibers in the retina is correlated with the occurrence of oligodendroglia. In the central nervous system, where myelinated fibers occur everywhere, the demonstration of the rôle of the oligodendroglia is more difficult. The medullated nerve fibers are always surrounded by the prolongations of the oligodendrocytes, and no oligodendroglia exist beyond the areas of myelinization. The only interstitial elements found in those portions of the retina that lack myelinated fibers were the cells of Mueller, the astrocytes and the microglia. Likewise, these are the only glia cells found in the normal human retina and in the retinas of animals in which myelinated fibers are not normally present.

It was of interest that the silver carbonate method showed the internal, limiting membrane of the retina not as a continuous structure but as a close meshwork of fine branches of processes of the cells of Mueller and of the astrocytes.

Further, the author states in his conclusions that the coexistence of myelinated fibers and of oligodendroglia in the retina of the rabbit lends strong support to del Rio Hortega's hypothesis that the oligodendrocytes either are primarily concerned in the secretion of myelin or assist in the elaboration of this substance. Further, it seems as if the forward migration of oligodendroglia cells in man is stopped at the lamina cribrosa (a structure not present in the eye of the rabbit). The lineal distribution of these cells in the optic nerve suggests this hypothesis. Therefore a faulty development of the lamina cribrosa (in man) or its delayed formation may be responsible for the occasional finding of medullated nerve fibers in the human eye.

SPAETH, Philadelphia.

HYPERTHYROIDISM ASSOCIATED WITH PARKINSONIAN SYNDROME. I. S. WECHSLER and NATHAN SAVITSKY, J. A. M. A. **97**:1283 (Oct. 31) 1931.

Wechsler and Savitsky note that the association of exophthalmic goiter with paralysis agitans is comparatively rare. Most of the cases reported in the literature show that the association is an accidental one. In the majority of instances the hyperthyroidism preceded the onset of the parkinsonian syndrome. In recent years, attention has been called to the presence of signs and symptoms referable to the vegetative nervous system in acute and in chronic encephalitis, which have a predilection for the basal ganglion-midbrain regions. But even before the involvement of the hypothalamic vegetative centers was recognized as the cause of metabolic and other disturbances, the sympathetic system was believed to be affected in exophthalmic goiter and to bear some relation to it. More recently, the suprarenals, the medulla of which is of the chromaffin sympathetic system, have been shown to stand in definite causal relation to hyperthyroidism. From time to time, suggestions have been made that physiologic or pathologic disturbances in the vegetative centers of the interbrain may have something to do with the production of many syndromes previously regarded as independent disease entities. The question, too, has been raised whether, in a syndrome such as hepatolenticular degeneration, the disease of the liver causes the changes in the brain or, conversely, the involvement of the striatum leads to secondary disturbances in the liver. In encephalitis it has long been known that what may be regarded as

dysthyroid symptoms were frequently a part of the clinical picture, even though there was no true exophthalmic goiter. The speculation is also justified as to whether the tremor of hyperthyroidism is not in effect the result of secondary changes in the striatum. In view of all this, the question now arises whether exophthalmic goiter may not in some way be the result of some altered physiologic state or pathologic change of the hypothalamic vegetative centers. The proximity of these structures to the regions affected in paralysis agitans and the occurrence of hyperthyroidism with parkinsonism in two cases reported by the authors in which the one syndrome preceded the other may possibly furnish clinical confirmation of theoretical views. In any event the cases, aside from their speculative interest, are worthy of record because of their clinical rarity. Of clinical interest in both the cases was the difficulty in dissociating the hyperthyroid from the parkinsonian tremor. The former is much finer and more rapid, but it overlaid the coarser and slower oscillations of basal ganglion origin. The improvement following thyroidectomy subtracted, as it were, the overtone of tremor and improved the underlying basal ganglion syndrome to some extent. But it may well be that the thyroidal tremor is in reality of basal ganglion origin and caused by toxic changes in those structures. It is interesting, too, that the surgeons hesitated to operate, and it was only after urging by the neurologist and assurance that the paralysis agitans in itself was no contraindication that operation was performed.

EDITOR'S ABSTRACT.

CONSIDERATIONS ON A CASE OF TUMOR OF THE ANTERIOR CRANIAL FOSSA IN A FEEBLEMINDED PATIENT WITH ENCEPHALOPATHY AND ACROMEGALY AND WITH INTEGRITY OF THE HYPOPHYSIS. CARMELO VENTRA, Arch. gen. di neurol., psichiat. e psicoanal. **12**:72 (March 31) 1931.

The author describes the case of a feebleminded epileptic woman. In early infancy she had meningitis and had become mentally defective; she learned to talk at 10 years, and always had a grave defect in speech. At the age of 15, on the background of mental deficiency, she began to show symptoms of mental disturbance. She began to menstruate only at 17, and the periods were irregular. She had a masculine aspect and presented symptoms of acromegaly. At the age of 30, she began to have severe generalized epileptic fits; later headache, vomiting, mental apathy and ophthalmoplegia developed. She died at the age of 45. At autopsy evidences of chronic leptopachymeningitis, especially at the base, with intense meningeal congestion were found. In the anterior cranial fossa, underneath the frontal lobes, there was a lobulated tumor, weighing 125 Gm., of the size of an orange. The hypophysis was normal. Histologic examination of the tumor revealed a glioma. Histologic examination of the hypophysis did not reveal an abnormality. After a detailed discussion of the case the author states that the diagnosis of intracranial tumors, difficult in general, becomes even more problematic in patients with mental disturbances, because of the difficulty of discriminating between symptoms due to the tumor and those due to the associated mental disease. Among the general symptoms of cerebral tumor, epilepsy of the essential type may develop early and for years remain the only symptom of a tumor. Essential epilepsy in such rare cases may be independent of the intracranial pressure and may be caused by the particular biocerebropathic conditions created by the tumor and of themselves sufficient to cause epilepsy. The facts that in the author's case the acromegaly became evident before the development of the tumor of the brain and that the hypophysis was found to be normal indicate that the acromegaly had no causal relationship to the tumor, and that an anatomic or neoplastic lesion of the hypophysis is not a necessary condition for the development of acromegaly. The author believes that the acromegaly in his case was due to the metaplastic anterior hyperpituitarism consecutive to the spreading of the inflammatory meningeal process localized particularly in the anterior cranial fossa. The coexistence of the tumor of the brain with the chronic meningitis and with the acromegaly suggests that in the pathogenesis of tumors of the brain several

factors concur; in particular, the neurohormonal factor as the cause of a disorderly and atypical development of tissues, and an irritative factor acting as a local stimulus for the active proliferation of the tissues.

YAKOVLEV, Palmer, Mass.

INTELLIGENCE AND DISEASE. By SHEPHERD DAWSON, Assisted by J. C. M.. CONN, Spec. Rep. Ser. No. 162, Medical Research Council, London, His Majesty's Stat. Off., 1931.

Dawson examined 1,077 children by means of the Binet intelligence tests. The findings were: 1. Children who were suffering from rheumatism, pneumonia, nephritis and other ailments described as "non-brain" did not differ in intelligence from the healthy members of the population to which they belonged; hence, disease on the whole does not appear to have any appreciable effect on intelligence. 2. Those who were suffering from disease of the spinal cord did not differ appreciably in intelligence from their healthy brothers and sisters. 3. On the whole, it was only in cases in which there was disease of the ductless glands and of the brain that there was appreciable departure from the normal in intelligence. 4. Localized cerebral disease, e. g., cerebral tumor, was sometimes unattended by intellectual deterioration. 5. Although spastic diplegia is usually accompanied by extreme dulness, there were cases in which there had apparently been no deterioration of intelligence. 6. The patients with chorea were neither more nor less intelligent than the rest of the subjects. 7. There was clear evidence of intellectual deterioration in most, but not all, of the cases of postencephalitis. There was no statistically significant difference between patients with the parkinsonian syndrome and those without it, or between those with behavior disturbance and those whose behavior was normal. The number of cases, however, was small, and caution must be exercised in generalizing from these observations. 8. The epileptic patients were, on the whole, of lower intelligence than their own brothers and sisters, and when they were retested showed signs of deterioration. There was a significant correlation between general improvement in the condition of these patients and their mental progress, but the observations suggested that from the severity and frequency of the fits no reliable inference could be made regarding the subsequent progress of the patient and that severity was the less reliable guide of the two; here, again, more observations are necessary. 9. In the acute stage of illness there was on the whole a slight improvement in mental efficiency. 10. Chronic illness did not appear to retard seriously the development of intelligence. 11. There was a significant correlation between the height and the intelligence ratio of the patients: those of higher intelligence tended to be slightly taller than the rest. 12. The children of higher intelligence had on the whole begun to walk and talk at an earlier age than the others.

SACHSE, Philadelphia.

OPTIC PATHWAYS IN A CASE OF CONGENITAL ANOPHTHALMOS. A. SOUQUES and IVAN BERTRAND, Rev. neurol. **2**:1 (July) 1931.

The clinical aspects of this case were reported by Souques in 1915. The patient finally died from general sepsis following pyelitis. No vestige of a retina was found in the orbit. The orbital portion of the optic nerve was reduced to a delicate filament, completely without medullated fibers and surrounded by a heavy sheath. The other nerves in the orbit were easily recognized, and the muscles appeared normal. The optic chiasm was formed by two delicate strands of tissue about the size of a normal trochlear nerve, and it contained no medullated nerve fibers. The optic tracts were much reduced, but Meynert's commissure was intact, although that of Gudden was not discerned. The external geniculate body was very small and malformed, small irregular cell groups being separated by considerable glial tissue and disappearance of the large ventral cells. The optic

radiation was scarcely visible. The stratum sagittale internum (optic radiation of Gratiolet) was much reduced. The thalamus, including the pulvinar, was entirely intact, and the association fibers of the occipital lobe were partially undeveloped. The occipital cortex presented interesting modifications. The white line of Gennari was present but so poorly defined as to resemble the usual appearance of the medullated stratum of Baillarger. It lay deeper than usual and, microscopically, was found to be very thin. Most of the radial fibers above this had disappeared, while those below showed slight rarefaction. The tangential stratum of Exner appeared entirely normal. The striated cortex was reduced by one third, all strata being affected but particularly the deeper ones. Strata IVb and VIa were particularly dense, owing to the apposition of ganglion cells. Stratum IVb included numerous giant cells. The area striata presented a normal extent. The parastriate field was not notably affected.

The authors believe that in this case, although the condition occurred in two brothers of a family, an infectious process during early life caused the resorption of the optic vesicle, and that the structures directly dependent on this vesicle underwent complete atrophy, whereas those more or less distantly related to it showed less severe changes. This case then is not one of complete agenesis of the visual system.

FREEMAN, Washington, D. C.

TREATMENT BY MALARIA IN ASYMPTOMATIC NEUROSYPHILIS. P. A. O'LEARY, J. A. M. A. **97**:1585 (Nov. 28) 1931.

The results of treatment by malaria in a group of cases of asymptomatic neurosyphilis are reported. The basis for the report is a series of fifty-eight patients, eighteen of whom were women and forty of whom were men. The first of these patients was inoculated with Plasmodium vivax in October, 1924, and the last inoculation was made in February, 1930; the observation periods following treatment, therefore, extended from one to six and a half years. In the group are included a few cases in which the neurosyphilis was recognized during the secondary manifestations of the disease but in which four courses of arsphenamine in conjunction with intensive treatment by mercury, bismuth and iodine did not materially improve the condition of the spinal fluid. In a second group, treatment was started while the patient was in the so-called latent or quiescent period of the disease, within the first five years of the infection, and after examination of the spinal fluid revealed that it was resistant to the usual treatment; the third and largest group includes patients in whom syphilis had been known to exist for periods varying from six to twenty-three years, who had received much intravenous and intramuscular treatment, and whose spinal fluid remained positive or reverted to positive when the patient was placed under observation without treatment. In twenty of the fifty-eight cases the condition of the spinal fluid was completely reversed to normal following treatment by malaria. It is significant that in thirteen of these twenty cases between twenty-four and forty-six injections of arsphenamine of various types had been given with corresponding amounts of mercury and bismuth, before treatment by malaria was instituted; only in five of these twenty cases was antisyphilitic medication given following the course of malaria. In an additional eight cases, all the factors in the spinal fluid were reversed to negative except the Wassermann reaction (Kolmer modification), which remained positive in varying strengths. It is evident from this study that treatment by malaria is the outstanding agent for the prevention of parenchymatous neurosyphilis after a trial with the usual measures of treatment has failed.

EDITOR'S ABSTRACT.

SENSORY DISCHARGES IN SINGLE CUTANEOUS NERVE FIBERS. E. D. ADRIAN, M. CATTELL and H. HOAGLAND, J. Physiol. **72**:377, 1931.

A new method of studying the impulse discharges in single nerve fibers from the tactile receptors in the skin is described. Preparations of the dorsal cutaneous

nerves of the frog are used. Many of these nerves contain a single fiber which has divided near the cord and sent branches into two nerve trunks. In stimulation of the receptive skin area supplied by one branch, antidromic impulses pass down the other branch and can be recorded in the nerve trunk in which it runs. The skin area supplied by a single fiber of the dorsal cutaneous nerves varies from 4 to 100 sq. mm., but in a given preparation the area remains constant despite various physiologic changes induced in the frog. There is considerable overlapping of the areas supplied by different fibers, but no evidence of a peripheral network common to several fibers.

The tactile endings become adapted very rapidly: impulses are only set up during the actual movement of the skin and a very slow movement may fail to exite. Skin vibration caused by an intermittent air blast produces discharges of long duration and high frequency. The frequency of discharge in a single nerve fiber may be as high as from 200 to 300 per second. This approaches the maximum frequency which the fibers can carry. The view put forward previously, that the sensory endings have a longer absolute refractory period than their nerve fibers, is incorrect.

Stimulation with an air blast interrupted at a high frequency does not give rise to pain reactions in an intact or decerebrate frog, in spite of the maximal discharge that would be set up in the sensory fibers. Thus the endings responding to this form of stimulation do not produce pain when the discharge frequency is very high. The endings in question are situated in the epidermis, for the discharge can no longer be obtained after this has been scraped away. This treatment sets up a continued discharge by slow impulses indistinguishable from those produced by acid on the skin.

ALPERS, Philadelphia.

NEURALGIA OF THE PHRENIC NERVE. HENRY MARCUS, Rev. neurol. **2**:21 (July) 1931.

That the phrenic nerve contains sensory branches innervating the pleura, pericardium and thymic regions is extremely probable, especially in view of Foerster's excellent work on the sensory pathways. Nevertheless, the diagnosis of phrenic neuralgia is seldom made and should not be made unless there is absence of disturbances of movement, sensibility and reflexes. Symptoms due to irritation of the phrenic nerve as by a fractured clavicle, cervical adenitis, tumors or pleurisy are apparently not uncommon.

Marcus reports the occurrence of the condition in himself and abstracts five other cases. The patient was of gouty diathesis and suffered cervical neuralgia following a chill in 1912. Two years after the fracture of a rib in 1916, violent pains occurred in the cervicoscapular region, especially on the right, radiating down the chest and the back and some being in the interior of the chest. This was followed by difficulty in swallowing and pain in the esophageal region, and at the same time by disturbing hiccup. Several days later, typical herpetic vesicles appeared above the spine of the right scapula. In 1924, there developed a serious disturbance of the stomach, with pain and heaviness and tenderness persisting for several months and disappearing eventually. Examination gave entirely negative results. Minor acute attacks were brought on in 1926 and 1927 by the eating of ices. These were followed by paroxysmal pain suggesting angina pectoris. Further paroxysms were caused by a movement of the shoulder, by walking and by changing positions, especially during the earliest part of sleep. Walking indoors was not followed by these pains, whereas cold air provoked them and drinking cold water regularly brought them on. The skin and muscles over the anterior portion of the thorax and neck sometimes became infiltrated. The whole syndrome slowly passed, but up until 1930 could still be brought on by cold.

FREEMAN, Washington, D. C.

OBSERVATIONS ON THE ETIOLOGICAL RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA: IV. A BIOLOGIC ASSAY OF THE GASTRIC SECRETION OF PATIENTS WITH PERNICIOUS ANEMIA HAVING FREE HYDROCHLORIC ACID AND THAT OF PATIENTS WITHOUT ANEMIA OR WITH HYPOCHROMIC ANEMIA HAVING NO FREE HYDROCHLORIC ACID AND OF THE RÔLE OF INTESTINAL IMPERMEABILITY TO HEMATOPOIETIC SUBSTANCES IN PERNICIOUS ANEMIA. W. B. CASTLE, C. W. HEATH and M. B. STRAUSS, Am. J. M. Sc. **182**:741 (Dec.) 1931.

In previous studies, the hematopoietic effect of substances in pernicious anemia was found due to an interaction between a protein or closely related substance in the beef muscle (extrinsic factor) and a product secreted by the gastric mucosa (intrinsic factor). The apparently normal gastric juice of two patients with the blood picture of addisonian pernicious anemia was studied, with the expected result that the gastric juices were in reality deficient in the intrinsic factor. In a patient without pernicious anemia but with apparently defective gastric juice it was demonstrated that the intrinsic factor was present in the gastric juice. In the apparently defective gastric juice of three patients suffering from a hypochromic type of anemia, the intrinsic factor was also present. A third possible mechanism of deficiency in the nature of difficulty in the assimilation or further metabolism of the hematopoietic substance is suggested, especially in view of the association of the condition with chronic diarrhea and partial intestinal obstructions. Intestinal impermeability to the active principle may account for certain of the so-called "liver-resistant" cases of pernicious anemia.

In the gastric contents of all patients with pernicious anemia in relapse, the essential intrinsic factor was found to be absent. In the body of the article, a general explanation of the natural course of the disease and of the age incidence is posited; it is well worth while for a further fundamental understanding of pernicious anemia.

MICHAELS, Detroit.

AN ANALYSIS OF THE SCHIZOPHRENIA PROBLEM FROM THE STANDPOINT OF THE INVESTIGATOR. R. G. HOSKINS, J. A. M. A. **97**:682 (Sept. 5) 1931.

The author states that the major problem confronting the investigator in schizophrenia is to characterize more adequately the psychosis itself. The term "dementia praecox" is a notably loose one and may well comprehend numerous more or less independent syndromes. The term is, perhaps, comparable with the word "fever," which may signify pneumonia, typhoid, acute arthritis, or what not. It is believed that technics are now available for the definite characterization of the psychosis if it is an entity, or for the subdivision of the general group into valid subentities, if such exist. What is needed to these ends is the accumulation of an adequate number of quantitative data on the various aspects of the disorder, with sufficiently searching statistical elaboration of the data to permit recognition and segregation of the characteristic, as contrasted with adventitious, phenomena. Much more rapid progress in research is to be anticipated if one deals with entities as such. If or when the possibility is realized of segregating the general mass of schizophrenic patients into explicit subgroups, no doubt the strategic aspects of the problem will change. Overfrequent annoyance of the subject with a variety of trying diagnostic procedures is undesirable; his recovery might be impeded thereby, and if he were kept in an overwrought condition, the various observations would not be representative. Actually, the number of procedures in which a given patient can participate without significant detriment must be determined in each case individually. It is not essential to insure statistical utility of the data that each patient be represented in all series of observations, provided systematic overlapping is practiced and an adequate number of individual observations are made.

EDITOR'S ABSTRACT.

PSYCHONEUROSES IN COLLEGE STUDENTS. A. C. CHESTOVICH, Rev. psychiat., neurol. & reflexol. (Leningrad) **5**:40, 1930.

The City Health Clinic of Moscow had the opportunity to examine college students who were referred by the college authorities before they could take a leave of absence or change their courses. One thousand students were examined, and of this number 89 per cent showed some degree of psychoneurosis associated with physical disorders such as anemias, undernourishment, early tuberculosis, etc. Twenty per cent of the patients showed a neurosis not associated with any illness. The cases in which the neurosis was complicated by or was complicating a definite somatic disorder were not analyzed in this study. The neurosis was definitely associated with difficulty in maintaining scholastic standing. A study of the personality of the students showed that they were maladjusted young men and women who were poorly prepared for their work, with a marked feeling of inferiority, and who were not able to cope with the difficult program of a university course. During the examination, the students pointed out the difficult situations with which they had to cope during the year. The neurosis offered an opportunity to leave the higher technical school and to maintain self-respect. (I suppose that the author has in mind the large number of young men and women who found access to the higher technical schools straight from the factories, due to the unprecedented demand for technical skill in the Soviet Union.) The author points out the extremely superficial level at which the work with the students was done. Sex problems are of definite etiologic significance, especially on account of the fluctuating standards and values giving rise to serious conflicts and to states of fear and anxiety. The author believes that only very intensive, individual work with the student is of value.

KASANIN, Boston.

LATE RIGIDITY IN THE PONTOCEREBELLAR TYPES OF PSEUDOBULBAR PALSY. L. VAN BOGAERT and IVAN BERTRAND, Rev. neurol. **2**:617 (Dec.) 1930.

Two cases, one with necropsy, are described in which there was development of general rigidity of all the limbs, coming on gradually after a series of small attacks. This was associated with some parkinsonian tremor, marked contractures, cogwheel phenomena and psychic "pillow," with exaggerated reflexes and a bilateral Babinski sign. Spontaneous sucking movements and spasmodic crying were observed, together with reflex grasping in one. Sensory disturbances were not marked, and there seemed to be no disturbance in language. One of the patients had, in addition, myoclonus of the palate and face, with involuntary movements of the left hand. Necropsy in this case revealed lesions that were particularly prominent in the pons, the whole ventral portion being more or less disintegrated, and several small foci in the tegmentum. The pyramidal tract was completely degenerated below this, and the middle cerebellar peduncles were gravely affected. The right olivary body showed hypertrophic degeneration, and there was a corresponding focus in the left dentate nucleus.

The authors explain the rigidity by the more or less complete deafferentation of the cerebellum and blockage of the pyramidal tract. They conclude that the bilateral destruction of a sufficient number of afferent spinocerebellar fibers may bring out a rigid syndrome that is difficult to differentiate from the rigidities due to lesions of the central gray nuclei. Tonic centers would seem to be released from inhibition and would be all the more active for destruction of the pyramidal tract.

FREEMAN, Washington, D. C.

THE SYMPATHETIC INNERVATION OF THE STOMACH. III. THE INTERACTION OF THE VAGUS AND SYMPATHETIC NERVES. B. A. MCSWINEY and J. M. ROBSON, J. Physiol. **73**:141, 1931.

Preparations of smooth muscle obtained from the fundus of the cat stomach with a dual innervation of vagus and sympathetic nerves were utilized. Experiments are described which demonstrate that the contraction of smooth muscle

following stimulation of the periarterial nerves may be reversed by stimulation of the vagus nerves. The reversal phenomena may be shown in three ways: (a) stimulation of periarterial nerves during the contraction produced by tetanization of the vagus nerve; (b) stimulation of periarterial nerves during vagus stimulation when the lever has returned to the previous base line through apparent fatigue of the muscle to vagus stimulation; (c) stimulation of the periarterial nerves which under ordinary conditions has no effect on the muscle may, during vagus stimulation, produce relaxation.

The time intervals in these experiments rule out the possibility of interference phenomena of the Wedensky type. The length of the muscle does not appear to be of any importance, as reversal may be obtained with the muscle at its resting length. It may be suggested that one set of muscle fibers is responsible for contraction and others for relaxation, but as no observations were made on this point the authors express no opinion concerning it.

Evidence is advanced to show that the type of response resulting from nerve stimulation is determined by the liberation of chemical substances in the periphery.

ALPERS, Philadelphia.

SEROLOGIC RESULTS IN MALARIALLY TREATED GENERAL PARALYSIS. J. ERNEST NICOLE and E. J. FITZGERALD, Am. J. Syph. **15**:496 (Oct.) 1931.

Reports of the serologic results of malarial treatment have been vague; time elements have been neglected and confirmatory tests lacking. The authors propose to clarify the problem by a simple statistical analysis of their results in the treatment of several hundred cases by this technic.

In two thirds of the cases persons with untreated dementia paralytica gave cell counts of over 20—most of them over 40. After malarial treatment, three fourths of them had a cell count under 10. Globulin tests, positive in 94 per cent of untreated cases, were positive in only 58 per cent—and by the end of three years in only 47 per cent—following therapy. The Boltz test was positive in 83 per cent of untreated patients; after treatment the percentage of positive reports diminished each year, falling under 11 per cent by the fourth year. The readings for colloidal gold are surveyed according to the highest figure reached. Practically every case reached a "5" in the curve before treatment; after malaria, 40 per cent never showed high points above "3"; after three years the number for whom low curves were found was 77 per cent. The positive Wassermann reactions of the spinal fluid were reduced by treatment from 100 to 68 per cent. The time factor here was not well analyzed. In some cases the spinal fluid became normal in every respect after treatment, but the serologic condition bore no relation to clinical improvement. A fifth of the patients gave a history of injury of the head.

DAVIDSON, Newark, N. J.

SUBOCCIPITAL DRAINAGE IN CASES OF INTRACRANIAL TRAUMA. F. ODY, Rev. neurol. **2**:28 (July) 1930.

The author stresses the ineffectuality of some of the operative interventions in cases of craniocerebral trauma, a fact observed by many different authors. The reason for the ineffectuality of lumbar puncture and of subtemporal decompression seems to be that in cases of fracture about the base there is inadequate communication between the posterior fossa and either the cranial cavity in general or the spinal spaces, owing to an effusion of blood with clots in the posterior fossa. It is not sufficient, he says, to observe a patient in a serious condition to warrant suboccipital craniectomy with drainage, but the aggravation of the state of the patient must be the guiding factor. "Il faut savoir attendre." Indications for suboccipital operation in these cases are those based on signs of medullary compression, particularly arterial hypertension with bradycardia giving way to hypotension and tachycardia, stertor, coma and early choked disks.

The author reports four cases of basilar fracture in which the operation mentioned was done; there were three recoveries and one death. On incising the

dura in the posterior fossa he invariably found blood-stained fluid with clots, under high pressure, and he reports the evacuation of from 300 to 400 cc. of fluid. The drop in pulse rate and easing of respiration following this procedure were extremely rapid. In one case, in which drainage became blocked, symptoms of medullary compression again appeared and were relieved in the same manner by reopening the wound and establishing satisfactory drainage. In all these cases lumbar puncture had been carried out without improvement and without observing much elevation in pressure.

FREEMAN, Washington, D. C.

PRESENT DAY TRENDS IN THE TEACHING OF PSYCHIATRY. FRANKLIN G. EBAUGH, J. Nerv. & Ment. Dis. **73**:384 (April) 1931.

Psychiatric teaching, in spite of its increasing importance in the curriculums of class A medical schools, is far from fulfilling its obligations. There is little organized effort on the part of the medical profession to take care of the enormous load of mental disease in this country, consisting of 300,000 hospital patients, with 75,000 new admissions each year. The author sent out a questionnaire to the 66 class A medical schools of the United States and received replies from 22 stating their increase in the amount of time devoted to the teaching of psychiatry. The total number of hours devoted by these 22 schools to psychiatry in 1920 was 743, with an average per school of 34 hours annually, whereas in 1929 and 1930 the number of hours had increased to 1,195 with an average of 54 hours annually. Of the 44 class A schools that did not reply, catalogs were obtainable in 40 instances, which showed that there was no provision for psychiatry in 2 schools, inadequate provision in 29 and adequate provision in 9. At the University of Colorado the psychobiologic point of view of Meyer has been adopted in such a way that the study of the patient's life situation is made, in preference to the erstwhile drilling in classification of mental disorder, and it is estimated that before graduation each student works out 50 cases. Psychiatry is no longer a mysterious specialty and must be within easy reach of the general practitioner to the extent that in the future he as well as the internist will have skill and interest in the early recognition of mental disease and will discover personality disorders in children as readily as he now can discover rickets.

HART, Greenwich, Conn.

NEURAXITIS FROM HERPES ZOSTER. CESARE BELLAVITIS, Riv. di neurol. **4**: 337 (Aug.) 1931.

The author reports the case of a patient, aged 53, with dementia praecox, in whom herpes zoster developed in the territory of the left second, third and fourth cervical roots. A few days later, when the cutaneous manifestations were disappearing, a left facial paralysis developed and a few days later a left hemiparesis, accompanied by mental confusion. Five months later, the patient died; at autopsy a diffuse congestion of the cerebrospinal axis was found. Histologic examination of the cervical ganglia showed an inflammatory process extending to the corresponding spinal roots. However, the process was not limited to the roots and to the ganglia, but invaded the cervical segments of the spinal cord, where congestion and perivascular infiltration were found both in the white and in the gray matter. In the gray matter the nerve cells were considerably involved, especially those in the posterior horns. The process extended also into the pons, the basal ganglia and the cortex. The lesions there also were of an inflammatory nature.

The author upholds, therefore, the conception of a zoster myelitis as first described by Brissaud and recently carefully investigated by Lhermitte and his co-workers. The author's conception departs from the old conception of herpes zoster as a ganglioradiculitis, the cutaneous manifestations of which are of a dystrophic nature, and substitutes for it the conception that makes of the zoster a superficial manifestation of a generalized neurotropic infection.

FERRARO, New York.

AN UNIDENTIFIED DEPRESSOR SUBSTANCE IN CERTAIN TISSUE EXTRACTS. U. S. v. EULER and J. H. GADDUM, J. Physiol. **72**:74 (June 6) 1931.

There are probably at least five different types of substance that may occur in tissue extracts and may produce vasodilatation: (1) histamine; (2) choline and choline esters; (3) substances allied to adenosine; (4) the depressor substance isolated by Kraut and Frey and called by them "Kalliknein," and (5) the unidentified substance with which this paper is concerned.

On making cold acid alcohol extracts of the various tissues obtained from horses, the authors noted the presence in these extracts, particularly in those from intestinal plain muscle and brain, of another unknown substance which lowers the arterial blood pressure of the atropinized rabbit by peripheral vasodilatation, and also stimulates the tone and rhythm of the rabbits' isolated intestine after atropine. This substance is dialyzable and filters under pressure through a cellophane membrane. It can be absorbed in benzoic acid and seems to be rather easily carried down by precipitants, suggesting that it is of a complicated nature. Tables of its solubility and stability are given. The effect on the blood pressure of the atropinized rabbit is due to peripheral vasodilatation, being produced equally well by direct injection into the aorta and with a shorter latent period than by intravenous injection.

Various experiments and methods of purification and measurements of depressor substances are described. It is not at present possible to devise simple and reliable pharmacologic tests that will measure the relative concentration of all these substances in a tissue extract.

ALPERS, Philadephia.

THE TREATMENT OF GENERAL PARALYSIS OF THE INSANE BY INDUCED MALARIA. ROBERT LEES, Brit. M. J. **2**:336 (Aug. 22) 1931.

Fifty patients (thirty-six adult and fourteen juvenile patients) suffering from either dementia paralytica or the tabetic form of dementia paralytica were treated by malaria, followed by tryparsamide, bismuth and other drugs. When the treatment was begun, none of the patients was certified as insane. Only a few were certifiable. During the course of the induced malaria, herpes labialis was common. Mental symptoms were aggravated in some cases during the rigors, and tabetic pains and crises were increased in severity. In the series, 28 per cent showed a satisfactory result, 54 per cent a poor result, and 18 per cent died. The cause of death in a number of cases could not be attributed to the malaria. Of the series, fourteen patients showed a complete remission of mental symptoms; three were unable to resume fully their former occupations because of tabetic symptoms. Of the fourteen successful cases, eight were adult and three juvenile cases of dementia paralytica, while three were cases of the tabetic form of dementia paralytica. The average period of observation in the successful cases following therapy was twenty-two months. In half of the successful cases the Wassermann reaction of the spinal fluid was negative; in nine the Wassermann reaction of the blood was positive, and in two the reaction of both blood and fluid was negative. In fourteen cases of juvenile dementia paralytica in which treatment was given, clinical recovery was 21.4 per cent, while the mortality was 14.3 per cent.

FERGUSON, Niagara Falls, N. Y.

A CLINICAL APPRAISAL OF SYPHILOPHOBIA. ROBERT GILMAN, Am. J. Syph. **15**:295 (July) 1931.

In the term "syphilophobia" Gilman includes not only a morbid dread of syphilis that becomes a consciousness-seizing anxiety, but also a medical self-analysis accompanied by devouring interest in the literature of this disease. He calls attention to the difference between propaganda about cancer and propaganda about syphilis; in the one open discussion, in the other vague reticence. The fact remains, in spite of the efforts of the medical profession, that syphilis still bears a venereal

stigma which makes public discussion of the problem difficult. Because of the way in which propaganda concerning syphilis are commonly distributed, most victims of syphilophobia are men. The causes are: introspective personality, casual sexual encounters, autosuggestion, attentive perusal of much quack "health" literature and often the discovery of a real or imagined symptom of syphilis. The underground dissemination of legends about syphilis is the most serious factor in the promotion of syphilophobia. To prevent it, Gilman follows Stokes in outlining certain principles in managing cases of suspected syphilis. A single positive Wassermann reaction should not be accepted as pathognomonic; serologic reports should not be given to laymen; laboratory results should be correlated with clinical data. Since gossip among the laity about this disease cannot be stopped, it should be made frank and honest by dissemination of correct information. Not until the public accepts syphilis as an illness rather than a vice will syphilophobia be eliminated.

DAVIDSON, Newark, N. J.

CHARACTERISTICS OF THE RETINAL MICROGLIA MIGRATED TO THE VITREOUS BODY. M. LOPEZ ENRIQUEZ and I. COSTERO, Bol. r. Soc. españ. de hist. nat. **31**:425, 1931.

Sections of the vitreous body of a human eye removed by operation in a case of glaucoma were cut with freezing microtome and stained with silver carbonate. Numerous microglia cells were observed in the vitreous body in the proximity of the retina. They differed from the normal microglia in that the cell bodies appeared flattened and oriented in a single plane, approximately at right angles to the inner surface of the retina. The microglia cells did not contain phagocystosed elements or show vacuolar alterations in their protoplasm. A second type of microglia cells was represented by elements of large size with numerous prolongations. These cells also were flat; their prolongations had ampullar dilatations occupied by large, irregular vacuoles. Similar cells have never been observed in the nervous system even in cases in which, as in the instance of the eye examined, marked changes of pressure had occurred.

A study of cultures of the microglia *in vitro* has permitted the interpretation of the abnormal forms described. It was found that similar types are abundant in these cultures. On fixation with an isotonic solution of 2 per cent formaldehyde, many of the cells acquire the ampullar swellings noticed in the cells occurring in the vitreous body. The authors' conclusion is that the peculiar shapes of the microglia cells in the vitreous body are due to the fluid environment in which they occur.

NONIDEZ, New York.

MACROGENITOSOMIA PRAECOX WITH HYDROCEPHALUS, DUE TO INFLAMMATORY LESIONS IN THE INFUNDIBULUM. A. THOMAS and H. SCHAEFFER, Rev. neurol. **2**:595 (Nov.) 1931.

A boy, aged 12 years, had had a large head at birth and had suffered from an acute infection, possibly meningitis, at 3 or 4 months, accompanied by several convulsive seizures. He was able to walk at 3 or 4 years. The present condition began with periodic, violent headaches and some vomiting. The head was large; there were bilateral spasticity and bilateral optic atrophy. He seemed well developed physically, but showed precocious development of the sexual organs, this development having occurred at the time of the onset of the headache. There was no polyuria, narcolepsy or glycosuria, and the spinal fluid was normal. The methylene blue test showed no penetration from the ventricles to the spinal canal. Meningitis, limited to the spinal canal, developed, and the child died. At autopsy the infundibular region was the seat of marked thickening and fibrosis, and there was general overgrowth of the glial tissue, accompanied by inflammatory lesions beneath the ependyma lining the third ventricle. In addition, there was a low grade meningitis completely blocking the spinal canal in the cervical region, with suppurative meningitis below this. The hypophysis was flattened, but appeared

normal; the thyroid and suprarenals likewise were normal. The testes weighed 30 Gm. and appeared completely developed. There was nothing abnormal in the region of the epiphysis.

FREEMAN, Washington, D. C.

TUMORS OF THE SUPRARENAL GLAND WITH SPECIAL REFERENCE TO CARCINOMA OF THE CORTEX. JACOB MEYER and GERALD FRUMESS, Arch. Int. Med. **48**:611 (Oct.) 1931.

Carcinoma of the suprarenal cortex is infrequent; Meyer and Frumess report a case exhibiting Gallais' "suprarenal genital syndrome." Their patient, a girl aged 13, had the bodily development of a woman aged 20. The illness began acutely with pain in the chest and convulsions; the menses had ceased three months before admission. The girl had pubic hair of masculine distribution. The blood pressure was 158 systolic and 85 diastolic. The patient rapidly grew worse and died a week after admission. At autopsy, it was found that a carcinoma of the suprarenal cortex had compressed and largely replaced the left kidney; the right suprarenal gland was normal. The authors point out that the sexual alterations produced by hypertrophy of the suprarenal cortex are always in the direction of masculinization; the male exhibits precocious maturity, while the female shows an enlarged clitoris, masculine pubic hair and pseudohermaphroditism. As in the authors' case, most patients show hypertension, even though the involvement is limited to the cortex of the gland. Meyer and Frumess do not believe that hypernephroma of the kidney bears any basic relationship to suprarenal carcinoma. Early diagnosis of the tumor is important, because of its removability. In at least three cases in the literature, early surgical extirpation of the growth resulted in a return to normal sexual characteristics.

DAVIDSON, Newark, N. J.

THE LOCALIZATION OF POSTHEMIPLEGIC ATHETOSIS. MICHAEL KAMIN, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:177, 1931.

In a man, aged 78, with hemiplegia of the left side and severe sensory disturbances, including astereognosis, athetosis-like movements developed in the paralyzed limbs; this was more marked in the upper limb. The anatomic substratum for this hyperkinesia was an area of softening in the right cerebral hemisphere, extending from the postcentral convolution to the occipital lobe, and changes in the oral-most portion of the putamen, which were much more extensive than one would ordinarily expect in simple senile atrophy.

Kamin is certain that the cerebral cortex as the effector organ for voluntary movements is also the effector organ for the type of dyskinesia presented by this patient. He cites Marburg, according to whom choreatic or athetoid movements are attributable to a lesion anywhere in the course of the cerebrocerebellar pathway and brachium conjunctivae. If one bears in mind that most observers have found undoubted evidence that choreiform or athetoid movements may occur also in lesions of the striatum, it becomes obvious that in the presence of diffuse lesions in the brain it is impossible to determine which mechanism is to be held responsible for the occurrence of this type of disordered motility. To speak, therefore, in cases of this nature of "centers" for such abnormal movements is futile.

KESCHNER, New York.

LIPOID HISTIOCYTOSIS (NIEMANN-PICK'S DISEASE). H. G. PONCHER, Am. J. Dis. Child. **42**:77 (July) 1931.

A clinicopathologic report is given of one case, that of a boy infant, aged 18 months, who died in the hospital twenty-four hours after admission. A correct diagnosis was made prior to death. The striking picture of the disease is described in detail. A splenic puncture revealed the typical "foam cells" of lipoid histiocytosis; the results of this technical procedure clinched the diagnosis of the disease.

Reference is made to a possible relationship of Niemann-Pick's disease to amaurotic family idiocy, with the statement that both conditions may be manifestations in varying degrees and distributions of the same or similar disturbances in lipoid metabolism. The two conditions may be caused by a metabolic disorder that in one instance affects primarily the central nervous system (amaurotic idiocy), in another the visceral organs (Niemann-Pick's disease) and in occasional instances affects both systems. In the case reported there was no cherry red spot on the fundus of either eye, but pathologic studies of the brain by Dr. Hassin revealed the characteristic features of amaurotic idiocy. The brain had a glistening appearance and was waxy, due to the high content of lipoid.

Reference is made to the fact that thirteen of the seventeen reported cases of lipoid histiocytosis have come into the literature during the past five years.

LEAVITT, Philadelphia.

THE AFFECTIVE PSYCHOSES IN CHILDREN. J. KASANIN, Am. J. Psychiat. **10**:897 (May) 1931.

Although statistics show that manic-depressive psychoses are extremely rare in children, the incidence is probably somewhat high, owing to the tendency of many clinics to group manifestations of this disease as schizophrenia. Kasanin reports on ten children with affective psychoses. In his cases, a tendency to go from one mood disturbance to its opposite was uncommon, a mild but well defined state of elation or depression being characteristic. A manic disorder was represented by irritability, elation and overactivity, while general retardation with undertalkativeness characterized the depressions. Precipitating causes were usually found, but seemed to the observer to be trivial. Heredity seemed to play no part. In five of his ten patients there were serious anatomic or physical defects, which differentiated the subject from other children. A history of mismanagement of sex life was traced in most of the cases, but seemed to be of etiologic significance in only three. None of Kasanin's patients were suicidal. In the author's experience the outlook is poor; none of these children made adequate adjustments, and some showed definite intellectual retardation.

DAVIDSON, Newark, N. J.

POLIO-ENCEPHALITIS. PHILLIP E. ROTHMAN. Am. J. Dis. Child. **42**:124 (July) 1931.

The author takes exception to the etiology of this condition as described by Strümpell in 1885. He makes reference to the extremely far-reaching effect that Strümpell's description has had on much of the literature from his time on. The symptom complex that Strümpell describes has an abrupt onset, characterized by fever, vomiting, unilateral convulsions and stupor, and is followed by hemiplegia. Frequently jacksonian epilepsy, spasticity and athetosis subsequently develop. Rothman reviews and quotes the literature on this clinical syndrome, and his conclusions are that the condition is rarely caused by acute infectious poliomyelitis of the cerebrum—in other words, by polio-encephalitis—but that in the vast majority of cases this syndrome results from thrombosis of, or hemorrhage from, one of the cerebral arteries, or more rarely from congenital cerebral aneurysms.

No original work or investigation is reported in this article; it is a review of the literature and the expression of an opinion contrary to the original concept of Strümpell.

LEAVITT, Philadelphia.

SYDENHAM'S CHOREA. R. W. WAGGONER, Am. J. M. Sc. **182**:467 (Oct.) 1931.

Sydenham's chorea is reviewed in the usual medical fashion. The author mentions, in addition to a precipitating, infectious factor in the etiology, a predisposition in the nature of an inferior integration of the psychomotor, cerebellar mechanism. In the author's series of cases, there was evidence of rheumatic fever or

cardiac involvement in 50 per cent and an incidence ratio of two females to one male. The pathologic process is considered as a generalized encephalitis, which involves predominantly the basal ganglia and particularly the striatum. In treatment, mental and physical rest comes first, with a nourishing diet; then the elimination of foci of infection after the movements have ceased. Various methods are discussed which the author believes have not been substantiated by different workers.

MICHAELS, Detroit.

OBSERVATIONS AND EXPERIMENTS ON THE RÔLE OF INSTINCT IN THE CHILD. F. H. G. VAN LOON, J. de neurol. et de psychiat. **31**:309 (May) 1931.

The author defines instinct as a psychologic entity, which differs in its nature and manifestations from every other mechanism or psychic function, especially from intelligence, even if the constituents are absolutely the same. He states that instinctive functions in man are similar to those in animals. He concludes that the solution of each new problem by the child is associated with a certain degree of evolution, which concerns the relative intensity of instinct and intelligence. It is impossible to say at what stage infants first show evidence of intellect. At a more advanced age, they still lack understanding and intellect, because their capacities are not yet sufficient to repel satisfactorily their instinctive tendencies and mechanisms, or to vary them to fit their needs.

WAGGONER, Ann Arbor, Mich.

UNILATERAL INSTABILITY OF THE PRESSURE IN THE RETINAL ARTERIES IN A SYMPATHETIC HEMI-EXCITATION SYNDROME. H. TILLÉ, Ann. d'ocul. **168**:278 (April) 1931.

Unilateral instability of the pressure in the retinal arteries was noted by Tillé in a patient, aged 31, in whom there was hemi-excitation of the sympathetic nervous system. He had violent attacks of pain occurring several times a day in the left side of the face. The left half of the body became alternately pale and flushed, and perspiration on this side was also increased. Neurologic examination otherwise gave negative results. Marked instability in the pressure in the retinal arteries of the left eye was evident not only during the course of one examination, but also from day to day. The pressure in the retinal arteries varied only slightly in the right eye. There was no fluctuation in the intra-ocular pressure in either eye.

BERENS, New York.

REBOUND AND INTRACENTRAL COMPETITION BETWEEN INHIBITORY AND STIMULATING IMPULSES. E. BRUECKE, C. HOU and E. KRANNICH, Arch. f. d. ges. Physiol. **227**:732, 1931.

The rebound contraction of the extensor of the knee which follows the flexor reflex if one stimulates the centripetal fibers of the sciatic nerve is due to an excitation of stimulating centripetal fibers in the sciatic nerve, besides the fibers that inhibit the extensor. This is proved by the fact that the afferent inhibitory fibers have a different chronaxia than the afferent fibers that produce the rebound. The stimulation of this latter group lasts longer than that of the inhibitory fibers, and thus the rebound is produced. In some cases a "rebound relaxation" of the extensor followed the flexor reflex. (The experiments were made on decerebrated cats.)

SPIEGEL, Philadelphia.

MENTAL HYGIENE IN SOVIET INDUSTRY. LUCIEN ZACHAROFF, Ment. Hyg. **15**:522 (July) 1931.

To reduce the deteriorating effect on workers' efficiency produced by hurry, worry and tension, the psychiatrists of Soviet Russia have been organized into a unified corps. A widespread group of dispensaries subject workers to medical

and psychiatric observation and provide for the issuance of "health passports" at short intervals. These examinations often reveal tendencies to mental aberration or pathologic adjustment. When such difficulties are located, effort is made to bring about relief; if necessary, the living conditions, vocational duties and even the domestic environment are properly modified. The slogan for mental hygiene work in Soviet industry, Zacharoff says, is "a united front for the establishment of a new, healthy society!"

DAVIDSON, Newark, N. J.

DIPLOPIA WITHOUT APPARENT LIMITATION OF OCULAR MOVEMENTS: RAPID RECOVERY AFTER THE REMOVAL OF A NASAL TUMOR. GENET and JACOD, Ann. d'ocul. **168**:669 (Aug.) 1931.

Genet and Jacod report a case in which diplopia developed in a patient in whom the only possible physical cause for the paresis of the left external rectus was a tumor in the nasopharynx. The diplopia and the paresis of the rectus disappeared the day following the removal of the tumor. The authors call attention to the fact that paresis of the oculomotor nerves is of longer duration when associated with infection in the nasal sinuses, and they believe that congestion was the probable cause of the paresis in their case.

BERENS, New York.

THE PRESENCE OF BILIRUBIN IN THE SPINAL FLUID. FRITZ LICKIUT, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:291 (Sept.) 1931.

Normally there is no bilirubin in the spinal fluid, except in the new-born as the result on icterus neonatorum, and also as a result of postnatal meningeal hemorrhage. In pathologic conditions it is found in all diseases with jaundice—catarrhal jaundice, acute yellow atrophy of the liver, tumor of the gallbladder, cirrhosis of the liver, etc. In meningitides—epidemic meningitis or tuberculous meningitis—traces of bilirubin may be found as an expression of injury of the blood-spinal fluid barrier.

ALPERS, Philadelphia.

THE CONDUCTION OF A NERVE IMPULSE WITH A DECREMENT. A. LANCZOS, Arch. f. d. ges Physiol. **228**:344, 1931.

In experiments on the sciatic nerve of large Hungarian frogs, a part of the nerve was paralyzed by a solution of potassium chloride. The changes of excitability and conductivity were studied by simple mechanical stimulation to avoid mistakes due to electric stimulation (spreading currents). These experiments show that the nerve impulse is conducted with a decrement in the paralyzed nerve according to the former results of Verworn and Lucas and Adrian.

SPIEGEL, Philadelphia.

DISSEMINATED ENCEPHALO-MYELITIS FOLLOWING SPINAL ANAESTHESIA. T. KAY MACLACHLAN, Brit. M. J. **2**:11 (July 4) 1931.

Two cases of encephalomyelitis with extensive neurologic complications following spinal anesthesia with benzoyldimethylamino-ethylpropenol hydrochloride are reported. The symptoms in both were of such a nature that they might be diagnosed as disseminated sclerosis. The author thinks, however, that the onset of the symptoms so soon (in the first case four days, and in the second a few days) after spinal anesthesia suggests that "their relationship to the anaesthesia is more than merely fortuitous."

FERGUSON, Niagara Falls, N. Y.

EFFECT OF STRYCHNINE ON MUSCLE TONUS. FROMENT, ROUGIER and MORELON, Rev. neurol. **1**:617 (May) 1931.

Strychnine sulphate in moderate to large doses increases the rigidity of pyramidal hypertonus, but reduces that of parkinsonism. It corrects the hypotonus of chorea and has a quieting effect on the involuntary movements. The authors

explain these divergent results by direct or indirect neural stimulation. Froment uses this as an additional indication of the fundamental difference between pyramidal and extrapyramidal hypertonus.

FREEMAN, Washington, D. C.

ASYMMETRIC SUSCEPTIBILITY TO THE ALTERNATING CURRENT. P. P. PAWLOFF and A. N. ZWETKOFF, J. f. Psychol. u. Neurol. **42**:477 (June) 1931.

An examination of the threshold of sensibility of the index fingers of right-handed, as well as of left-handed persons to the alternating current revealed a higher threshold in the left index finger in right-handed persons and a higher threshold in the right index finger in left-handed persons. The authors do not attempt to offer an explanation for this asymmetry until they have examined more subjects as well as the other fingers and hands.

KESCHNER, New York.

THE RELATION OF BROCA'S CENTER TO LEFTHANDEDNESS. KARL ROTHSCHILD, Am. J. M. Sc. **182**:116 (July) 1931.

From two cases observed by the author he concludes that the location of the speech center and the preference for one side of the body stand in only loose connection, and that the location of Broca's center in the right hemisphere is compatible with right handedness. To warrant these considerations, more detailed study of the cases should be presented.

MICHAELS, Detroit.

SYMPTOMS OF HYPOPHYSEAL TUMORS. BRETAGNE and MICHON, Ann. d'ocul. **168**:592 (July) 1931.

Bretagne and Michon call attention to two symptoms of hypophyseal tumors. In one case, bilateral excessive lacrimation was a troublesome symptom and preceded the other symptoms of hypophyseal tumor by two years. In another case, that of a woman, aged 27, a dry eye was complained of during the development of a hypophyseal tumor.

BERENS, New York.

HEREDITY AND DUPUYTREN'S CONTRACTION. J. S. MANSON, Brit. M. J. **2**:11 (July 4) 1931.

Hardening and contraction of the palmar fascia were found to occur in three brothers whose father was also affected and whose mother was affected by a double-bent little finger at the proximal interphalangeal joint, but whose other fingers were normal. The third generation, ranging in age from 41 to 33, is unaffected.

FERGUSON, Niagara Falls, N. Y.

INFLUENCE OF STIMULATION OF THE SYMPATHETIC ON THE RETINA. S. KOGO, Arch. f. d. ges. Physiol. **227**:727, 1931.

The author was again unable to prove the theory of Hess that suspects an influence of the sympathetic on the retina. The histologic picture of the retina on the side of the stimulation of the sympathetic was the same as that on the nodmal side.

THE INFLUENCE OF HIGHER CENTERS ON THE CONDUCTION IN PERIPHERAL NERVES. H. ROSENBERG and O. SAGER, Arch. f. d. ges. Physiol. **228**:423, 1931.

The speed of conduction in the nervus ischiadicus was examined before and after the extirpation of the lobi optici in frogs. An increase of the speed of conduction was found (from 5.6 to 12.4 per cent).

SPIEGEL, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Secretary*

Three Hundred and Ninety-Sixth Meeting, Dec. 17, 1931

A. MYERSON, M.D., *Presiding*

THE ACTION OF CERTAIN DRUGS ON THE PRESSURES OF THE CEREBROSPINAL FLUID, INTERNAL JUGULAR VEIN AND SYSTEMIC ARTERIES OF MAN. DR. JULIUS LOMAN and DR. A. MYERSON.

This article appeared in full in the May, 1932, issue of the ARCHIVES.

DISCUSSION

DR. JOSEPH LOONEY: It seems to me that it is possible that the disagreement as to the results produced by pituitary is due to the fact that the ordinary preparation on the market is comprised of two different principles, pitressin and pitocin. Would there not be a more consistent result if these two drugs were used separately? It is possible that preparations from different companies show a preponderance of one or the other principle to a greater or less degree.

DR. FRANK FREMONT-SMITH: Another factor that may explain the discrepancy between these results and those obtained in animals may be the anesthetic employed in animal experiments. Thus, histamine appears to cause a fall in spinal fluid pressure in animals under ether. With amytal, however, Forbes found that it caused a rise. Lenox and Weiss, and now Myerson, showed that it produces a rise of cerebrospinal fluid pressure in man also. The rise from histamine appears to be due to dilatation of cerebral vessels, as both the rise and the fall are rapid. I disagree with Dr. Myerson in interpreting the fall in spinal fluid pressure produced by caffeine as due to diuresis, for it seems hardly likely that diuresis could occur so promptly. Increased respiration due to caffeine might lower the cerebrospinal fluid pressure.

DR. J. B. AYER: Are all these patients from the state hospital, or are they patients with varying pathologic lesions?

DR. A. MYERSON: We used pituitary solution. The results on the whole were consistent. The action of histamine we believe to be vasodilatation and not an increase in the activity of the choroid plexus. In regard to caffeine, I thought at first that there was diuresis, but after hearing Dr. Fremont-Smith, I retract this statement. Answering Dr. Ayer, the patients at the state hospital had different kinds of psychoses, mostly dementia praecox, manic-depressive psychoses and dementia paralytica. They proved excellent subjects. No one can say what takes place following trauma.

THE CEREBRAL CIRCULATION: XVIII. EFFECT OF CAFFEINE ON THE CEREBRAL VESSELS. DR. JACOB FINESINGER.

This paper will be published in full in a later issue of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY.

THE WORCESTER STATE HOSPITAL RESEARCH PROJECT IN SCHIZOPHRENIA. DR. R. G. HOSKINS.

A collaborative investigation of the etiology and treatment of schizophrenia was begun in 1927. Two opposing counsels were considered in the formulation of the methodology. Influential psychiatric opinion holds that successful results are contingent on a study of "the problem as a whole." In practical terms this seems to imply the necessity of observations on a wide variety of aspects of the disorder and subsequent integration of the results. Psychiatric opinion seems to include a hiatus as to how the integration is best accomplished. Another opinion is that intensive studies of single aspects of the disorder are more likely to be productive. It has been attempted to realize the benefits of both plans simultaneously.

An extensive approach seems imperative because of the existing uncertainty of the actual composition of schizophrenia. Adequate definition of the disorder, if it is a unity, or a successful distribution into subentities, if they exist, amounts to a recognition of specific syndromes. The mathematical possibility of detecting these is in direct ratio with the number of features quantitatively recognized. An attempt has been made to profit by the fact that the greater the variety of observations made on any group of subjects the less is the *pro rata* cost of each. Furthermore, the greater the number of coincident observations, the greater are the possibilities of productive correlations.

Such evidence as hereditary tainting, predilection for constitutional types and the high proportion of double incidence of the disorder in monozygotic as compared with dizygotic twins indicates the existence of an organic liability factor. The disorder is more obviously characterized clinically, however, by psychologic abnormalities. If the organic factors are to be studied, the research necessarily becomes reduced to an attempt to correlate organic with psychologic happenings; this fact imposes the necessity of quantitative determinations of each, together with an empirical estimate of the variability of each characteristic investigated. The difficulties of the quantitative measurement of mentality or personality factors is recognized, but it is believed that adequate investigation will demonstrate the possibility of sufficiently accurate quantifications to permit productive correlations. An investigation of this possibility constitutes a specific subproject in the research.

The difficulty of the recruiting and organizing of an adequate personnel was foreseen, but proved to be not insurmountable. A staff has been assembled that is noteworthy in its loyalty, cooperativeness and intelligent initiative. The members show every evidence of appreciation of unusual facilities for immediate productive investment of time and energy.

The research staff consists of a director, an assistant director, four psychiatrists, two ward observers, a special social service investigator, two observers trained in occupational therapeutics, a chief of laboratories, a pathologist, seven laboratory technicians, two internists, a dentist, a consultant roentgenologist, an x-ray technician, a chief and an assistant psychologist, six psychometrists, a chief statistician, two assistant statisticians, four statistical clerks, a supervisor of nurses, eight ward nurses, twelve ward attendants, a secretary and five stenographic clerks. The service is organized as an independent but closely integrating department of the hospital.

The routine studies consist of the taking of a detailed social history, searching physical examination, quantitative determination of forty metabolic characteristics, fourteen psychometric tests, twelve determinations of psychomotor functions and special observations incident to the study of autonomic activity and vasomotor efficiency. Special allied projects are the study of blood grouping and that of anthropometry. Dental examinations and roentgenologic studies of the chest, sella turcica and sinuses and of the gastro-intestinal motor functions are also made. Each patient is under the constant study of a psychiatrist who files detailed daily notes during the test periods and weekly notes in the intervals between tests. Each patient is given three consecutive study periods of five weeks each with three

week intervals between studies. After this preliminary study the patient is given appropriate therapy, and the various examinations are repeated at suitable intervals.

The project has been gratifyingly productive of observations made under comparable conditions permitting searching statistical analysis. The accumulated data have been reported in part. A considerable number of other reports are in press, in preparation or in prospect.

DISCUSSION

DR. D. GREGG: I am wondering if any attempt has been made to study the relation between the patient's constitutional make-up and the accident, infection or whatever leads to the loss of adaptation.

DR. K. J. TILLOTSON: It is not known what schizophrenia is. It is difficult to devise methods for the study of a subject about which so little is known. As an executive and psychiatrist, I wish to ask whether the personnel to which Dr. Hoskins refers are all devoting their entire time to this research project, or, if not, what part is devoted to it. Second, where are the results to be obtained from this variegated spectrum to be deduced? Are they to be compiled by the statistical machine at the state house? With so many factors to consider one might question the conclusions if this were the case.

DR. K. M. BOWMAN: The problem of schizophrenia is the most important one in psychiatry at this time. Those who undertake to study it should have adequate training in psychiatry. Hospitals for mental diseases are the only places where any elaborate program of research can be undertaken, and it is interesting to see that, more and more, well thought out plans of study and research are being worked out in the various hospitals for mental diseases.

Just how one should study the problem of schizophrenia is not easy to say, and I suppose everyone has different views as to what are the most important things to work out. With many fundamental ideas concerning the nature of this disorder unsolved, there is no way of knowing when some one may light on the clue that all are seeking and that will give a true understanding of the nature of this disorder.

On visiting the Worcester State Hospital a few weeks ago, I was much impressed by the work that was being done there. No one who has not seen it can appreciate what an enormous task it is simply to start such a research. Dr. Hoskins has tried to work out a plan for recording his statistical material in a quantitative fashion. We have been trying to do the same thing at the Boston Psychopathic Hospital in a study that we have been carrying on for the past few years. I might point out that there are various ways of recording such data quantitatively. For example, in Dr. Hoskins' scheme the number of delusions and hallucinations is recorded, whereas under our scheme at the Boston Psychopathic Hospital we have tried to divide delusions and hallucinations into different types and to list the number of types rather than the actual number of delusions. I mention this as showing merely how, in any quantitative scheme, there are a number of ways of recording the data, and that there may be considerable difference of opinion as to which is the best method.

DR. I. CORIAT: A serious omission in this plan of research is that of the dynamic approach to the problem of schizophrenia. One of the most important aspects of the problem of schizophrenia is the attitude of the patient's ego to reality, in which there is an attempt to mold reality according to wish and fantasy thinking. No matter how extensively the various tests can be carried out, they all rest on a statistical and descriptive basis and make no attempt to gain insight into the real mental mechanisms.

DR. J. KASANIN: The investigation at the Worcester Hospital was started shortly after that at the Psychopathic Hospital. At Worcester, the investigation is based on endocrine factors, and at the Psychopathic Hospital on psychologic and sociologic factors. Both institutions have developed various elements in common, especially in the field of methodology of the research. I hope that a better understanding and approach in this extremely difficult problem will be reached.

Dr. R. Hoskins: We have not yet investigated the relationship between the constitutional make-up and the operation of precipitating factors. We have attempted to gather data so that they can be analyzed according to different points of view. We have attempted to record the factors that Dr. Gregg has mentioned in the social history. We have a full time staff of about sixty persons. The statistical interpretation of results is not made at the state house. We have our own statistical department at the head of which is a man trained in ethnology, psychology and bionomics as well as in higher mathematics. The cost of schizophrenia to the United States in dollars and cents is well over a million dollars a day. A larger element is the social cost, the suffering that the disease causes to the patients and to others. I think that if any of the members of this society had a choice between schizophrenia and death for a member of his family he would prefer death. In reply to Dr. Bowman, the State Hospital is a gold mine of human biology. We have consulted the Psychopathic Hospital freely for ideas. We do attempt to differentiate types of delusions and hallucinations, but the records are in the case histories rather than in the consolidation forms. As to the dynamic approach, we are taking a dynamic approach to the disease, although not a freudian one. The aspects of the problem that we regard as most fundamental do not lend themselves to "dynamic" approach. If one has dementia praecox, it is because one was born with something that makes one have it. The "identical twins" statistics prove this. If one identical twin becomes schizophrenic, the other would do well to select his asylum. He has relatively little hope of escaping the disorder. Conditioning factors determine the coloring of the picture and are amenable to "analysis," but its existence is organically determined. The percentage of "cures" among patients treated by means of psychoanalysis is no higher, apparently, than that resulting from mere custodial care. More controlled evidence on this point is needed. The psychosis offers many clues for its solution. The prognosis for pernicious anemia was "hopeless" five years ago. It can now be treated successfully. There is no sound reason why one cannot hope ultimately for equally successful results in schizophrenia.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Dec. 18, 1931

Joseph McIver, M.D., *President, in the Chair*

Two Patients with Disturbance in Speech as a Sequel to Epidemic Encephalitis. Dr. Alfred Gordon.

In the course of epidemic encephalitis, and especially in postencephalitic parkinsonism, many varieties of ticlike movements and analogous hyperkinetic manifestations have been observed and described. Some are relatively frequent, such as oculogyric crises; other manifestations are more or less rare, such as speech disturbances. Since 1922, there have appeared occasionally in the literature cases in which the tongue was involved—propulsion followed by retreat of the tongue, frequently or continuously repeated. Smacking or continuously moistening the lips, contraction of the muscles of the tongue and vibratory or myoclonic contractions of the tongue have also been reported. The manifestations shown by the two patients I am presenting are exceptional. They concern the buccal cavity, the lips, the chin and especially the tongue, which renders speech unusual. They present an additional postencephalitic phenomenon among the large number already observed.

Case 1.—A girl, aged 17, began to observe a mild impediment of speech four years prior to presentation, following a slight febrile condition. This condition continued, becoming more and more pronounced, and for the last two years has been stationary. The present condition is as follows: In speaking, the tongue

has a tendency to protrude between the teeth. In the beginning of speech the tongue rolls, curls and protrudes, mostly on the right side. The muscles near the angles of the mouth and those of the chin contract more than the other muscles of the cheeks, so that two deep furrows appear on both sides of the mouth. It seems that all other muscles of the face remain mobile, while the muscles of the lips function. This is observed in the beginning of attempts to speak. Speech itself becomes indistinct; the tongue is always in the way. One may have the impression that the patient is stammering, but she is not. There is no evidence of aphasia, paraphasia, anarthria or dysarthria. While she is speaking, there is also noticeable a peculiar state of the lower jaw, namely, a tendency to droop, so that she frequently puts her hand under the chin to hold it up. While there is no paralysis of the tongue, as it can move in all directions, the food remains in the mouth for a long time, and at times there is difficulty in swallowing. The patient also complains of pronounced salivation. Examination of the buccal cavity fails to reveal any motor or sensory involvement of the muscles of the palate and pharynx.

About six months before presentation, the patient began to observe a gradually oncoming weakness of the right upper extremity. Examination revealed a certain amount of weakness of every segment of that limb and a fine tremor of the hand. She claims to have difficulty in threading a needle or doing other fine work.

Further examination showed increased knee jerks, but no pathologic reflexes. With regard to the serology, blood eyes, sphincters and sensations, there are no abnormalities.

Case 2.—A girl, aged 19, five years before presentation had an attack of depressive psychosis, from which she made a complete recovery. Two years prior to presentation, following a slight fever, a disorder in speech developed from which she still suffers. One year later, a tic of the eyelids developed. The onset, mode of development, progressive course and present state of the difficulty in speech are identical with those in the first case, except that they are more pronounced. The position of the tongue and the condition of the muscles of the angle of the mouth and of those of the chin are also the same as in the first case. In addition, the patient also complains that food and liquids run out of the mouth during mastication.

It is interesting to note that this patient, like the first one, presents a weakness of every segment of the right upper extremity. The grip of the right hand is 50 and of the left 60, although like the first patient she is right-handed. A detailed examination showed that in every other respect the patient is normal somatically.

If the two cases are postencephalitic, it should be presumed that the lesion lies in the striatum and presents the usual structural damage observed in encephalitis. A question arises as to the possibility of explaining the disorder in speech on this purely organic basis. It is indeed difficult to admit that a direct injury to the striate body could be the sole cause of so many somatic, vegetative and psychic manifestations. Close examination of the mode of speaking of these patients leads to the conception of a purposeful pattern, which originated four and two years ago, respectively, and which has remained up to the present. Both patients had difficulties of an affective character at the onset of the disorder, and as an outlet for the state of anxiety in which they found themselves developed a substitution phenomenon in the form of a compulsion neurosis.

Three Cases of Tabes Dorsalis with Unusual Findings. Dr. Emma B. Bevan.

Osteo-Arthropathies of the Spine in Tabes Dorsalis.—According to most writers, osteo-arthropathy of the spine is a rare complication in tabes dorsalis. Oppenheim described the sudden, painless onset of edema, followed by rapid destruction of the ends of the bones; at the same time there is new formation of bone—a diffuse and irregular protrusion of the ends of the joints, with bony excrescences and free bodies. The periarticular formation of new bone is characteristic. He added that "arthropathies of the vertebral column are rare in tabes."

Marie gave an interesting and instructive picture of the deformity of the vertebral column, its slow painless progress and the frequency with which arthropathies are complicated by fractures.

In 1902, Spiller, in surveying the literature, found a limited number of such cases reported and described a typical case of tabes with arthropathy of the spine, complicated by a similar involvement of several other joints. Five more cases were reported in America by Cornell, Campbell, Patrick, Holmes and Funstein between that time and 1927, when Garvey and Glass made another survey of the literature and reported four additional cases. At that time they stated that Charcot joint of the spine had been described only sixty times since its discovery by Charcot. Frank reported twenty-six cases in 1904; Rogers estimated the number of reported cases at sixty. In addition, one such case was reported from Berlin and six from America.

Garvey and Glass stated that in their opinion Charcot joint of the spine is more frequent than is recorded: "It is unknown to the patient because it gives him no symptoms and unknown to the physician who usually does not make an examination of the spine once he has established a diagnosis of tabes." To substantiate this theory they found in eight months, at the University Hospital in Ann Arbor, Mich., four definite cases of Charcot joint of the spine, with one suspected case. They made the following statements about their cases, which fit in well with those we are reporting: 1. As in our series, only males were affected. 2. Spinal lesions occurred late after the original syphilitic infection. 3. The condition was not noticed by the patient first. 4. Physical examination revealed definite findings over the spine. 5. The condition developed in spite of active antisyphilitic treatment. 6. Arthropathy of the spine was associated with arthropathies of other joints.

Case 1.—A white man was first admitted to the hospital in August, 1915, with characteristic signs and symptoms of tabes. He gave a history of syphilitic and gonorrheal infection in 1910. The Wassermann reaction of the blood was positive. The patient received considerable antisyphilitic treatment, and was then discharged. He returned in August, 1923, complaining of weakness in the right thigh, which was accompanied by marked swelling. The outstanding feature in the past medical history was that he had received a severe injury to the right knee in early childhood, which had resulted in ankylosis of the joint. In addition to this, he had been earning his living as a butcher, and had been jumping on and off a wagon, so that, with the ankylosis of the right knee, the repeated jar of landings was directly transmitted to the hip joint.

A roentgen examination in 1923 showed a tilting of the fourth lumbar on the fifth lumbar vertebra, with new bone bridging over between these vertebrae on both sides. There was considerable sclerosis of the fourth and fifth lumbar and first sacral vertebra; the head of the right femur was entirely gone, and the neck of the bone was resting on the lip of the acetabulum.

By means of roentgenograms, we have been able to follow the advance of the disease in spite of antisyphilitic treatment, until now, in addition to an involvement of the right hip, the patient has a characteristic Charcot joint of the spine and must use a wheel chair.

The latest roentgen examination, on Oct. 13, 1931, showed an old intracapsular fracture of the right femur. The shaft of the bone was displaced upward and showed some outward and backward rotation, the neck and greater portion of the head being completely absorbed. There was a large beak-shaped osteophyte projecting inward from the greater trochanter. There was a large osteophytic outgrowth at the inner portion of the shaft, approximately 3 cm. below the lesser trochanter. Projecting downward on the inner side of the femur was a large, somewhat wide, irregular piece of bone; the lower three lumbar vertebrae were markedly sclerotic. The interarticular cartilage between the fourth and fifth lumbar vertebrae was partially destroyed, and the articulating surface of these bones approximated more closely than normal. There were bridges of bones between these bones on both sides.

Cas 2.—The patient, with characteristic findings of tabes, has advanced osteoarthropathy of the spine, as shown by roentgenograms.

Paradoxical Pupillary Reaction to Light.—According to Oppenheim, two conditions may give the observer the impression that he is seeing a true paradoxical pupillary reflex to light: (1) a minimal, unnoticed contraction at the time of illumination followed by a dilatation; (2) the eyeballs at the moment of illumination pass into a position of divergence. He concedes, however, that when these two sources of possible error have been ruled out there are a limited number of cases in which a true paradoxical light reflex is present.

Spiller and Posey reported the paradoxical pupil as an exceedingly rare symptom in tabes, "if indeed, it really occurs." They believe that the "observed dilatation may be due to impairment of accommodation, or to a weakness of convergence," and that the sphincter of the iris first attempts to close and, being unable to do so, dilates. They did not think at that time that there was a genuine paradoxical light reflex in any case reported in the literature.

Poulard believed that this is a rare reaction which is poorly understood, and which occurs only in advanced cases.

A case of syringomyelia in which there was a paradoxical light reflex was reported by Elliott and Hogan. They quoted Curran as having told them in a personal communication that he had observed several such pupils since he had become interested in them. In his experience, he found that the paradoxical light reflex occurred in elderly persons, most of whom had had syphilis, though a few had multiple sclerosis.

In the recent German literature, Lowenstein reported a case of dementia paralytica "with light reactions at times normal in direction and at other times paradoxic." He mentioned the type of paradoxical light reflex, "(*a*) Bechterew and Westphal type, in which the pupillary dilatation is produced by a minimal contraction; (*b*) Kehser type in which dilatation occurs after a prolonged latent period; (*c*) a true paradoxical reaction—showing either a slow and inadequate or a prompt and adequate dilatation of the pupil to light stimulation." He believed that this division is not accurate, and that the various types are simply different phases of the same pathologic process. He observed his patient for a year and found all the aforementioned conditions present at different times.

Lowenstein also reported a case of tabes in which repeated stimulation with a weak illumination was required to produce a slight dilatation; the dilatation following the next stimulus was greater, and the third was greater than the previous ones. This is contrary to what occurred in a case reported by Spiller, who found that the paradoxical light reflex was not present constantly in his case, but was more likely to be found after the first illumination.

Case 3.—A young white woman, married, with three children, presents all of the classic signs of tabes, probably of congenital origin, and has positive signs in the blood and spinal fluid, with a tabetic colloidal gold curve. At times she shows a true paradoxical reaction to light; at times there is an unusual paradoxical reaction to light, and at other times the pupils remain absolutely fixed to light. She was examined by Dr. Deichler, but on that afternoon did not show the consensual paradoxical light reflex. His positive findings were: (*a*) slight widening of the palpebral fissure, especially on the right; (*b*) round, equal pupils which either do not react to light or dilate; (*c*) no consensual reflex in either eye, but active convergence and accommodation; (*d*) slight blurring to the nasal side of the disk margins, good color of nerve and prominent perivascular lymph spaces.

Fracture of the Cervical Vertebrae. Dr. Frederic H. Leavitt.

These two cases are presented to demonstrate that in serious injury or disease of the cervical vertebrae, in which a so-called "broken neck" resulted, the condition was successfully treated by palliative measures rather than by immediate surgical intervention.

Case 1.—E. J., a boy, aged 19, was in perfect health until he was thrown from an automobile in a collision and landed at the bottom of a stone quarry. When brought to the hospital, he obviously had a "broken neck" and was completely

paralyzed from the neck down. Immediate surgical procedures were proposed, as the x-ray showed a complete crush fracture of the bodies of the fifth and sixth cervical vertebrae. The medical staff decided to temporize, and within four days the patient's complete quadriplegia had changed into a Brown-Séquard syndrome, with complete motor paralysis of the left side of the body below the level of the clavicle, and sensory paralysis (essentially to pain and temperature) on the right. Two weeks later, power had returned to practically every group of muscles on the formerly paralyzed left side, and the sensory disturbances had become much less pronounced. Aside from the fracture of the right femur, which is now well united, the patient's condition is favorable.

CASE 2.—W. S., aged 58, was operated on in January, 1931, because of dysuria, a superpubic median bar prostatectomy being done; no evidences of malignancy were found. While convalescing from this operation his head suddenly dropped forward while he was sitting up in bed, and he became partially paralyzed in the arms and legs. A roentgenogram of the cervical vertebrae showed a destructive process involving the bodies of the third, fourth and fifth cervical vertebrae. The patient was placed on extension and within a few days much power returned, except for a slight weakness in the shoulder girdle group on both sides. Continued extension resulted in the formation of callus in the posterior region in the neck, and all motor and sensory disturbances below the level of the pathologic area in the neck disappeared. At the present time this patient walks about and attends to his slight duties while wearing a supporting Taylor neck and head brace. He feels comfortable and complains of no symptoms of motor or sensory weakness. The roentgenologic reports revealed a pathologic destruction of the bodies of the vertebrae, the nature of the process not being definitely determined, although it appeared to be neoplastic rather than tuberculous. All tests for syphilis in this case gave negative results.

DISCUSSION

DR. GEORGE WILSON: The management of injuries to the spinal column and cord is extremely important. If the spinal cord has been injured by a fracture or by a fracture dislocation I believe that no real good comes from an operation, no matter how early it may be done. In the neurologic service of the Philadelphia General Hospital there has recently been a man who had a fracture of one of the lower dorsal vertebrae and who was operated on two hours after the injury. The cord was crushed, and no recovery ensued. The man lived, so that no damage was done in this case. In a case of hematomyelia due to trauma and in which the spine has not been injured, it is my opinion that it is most important to withhold operation. I have observed a number of instances in which patients recovered completely after such a condition, as, for example, the patient presented by Dr. Lewis and myself before this Society last year. That case was one of hematomyelia in the cervical region, with signs of a complete block, which lasted for about five weeks. The question arose as to the advisability of an operation, especially in view of the fact that a block existed. The man was given extra nursing care and placed on a water bed; meticulous attention was paid to the urinary system and to the skin; complete recovery ensued. I have recently had a similar experience with a patient in the Episcopal Hospital.

DR. FRANCIS C. GRANT: Recently, I have operated in two cases of fracture dislocation in the cervical region, in one instance involving the fourth and fifth, and in the other the sixth and seventh, vertebrae. In both a complete transverse lesion of the cord, with a demonstrable block to the Queckenstedt test, was present. As these patients were seen within twelve hours after the injury, and because x-ray evidence of bony pressure on the cord and a block on lumbar puncture were noted, a decompressive laminectomy was promptly carried through under local anesthesia. Exposure of the cord showed that in neither instance was more than a marked localized edema present. The blood vessels on the posterior aspect of the cord appeared to be almost normal in size and distribution. Nothing suggesting extramedullary or intramedullary hemorrhage was seen. In spite of this prompt relief from pressure, an immediate pulmonary edema and high fever developed in both patients, one dying in twelve and the other in forty-eight hours.

In a third case, encountered two years ago, closed reduction of the fracture by Taylor's method was successfully carried through, but again pulmonary edema appeared, and death occurred on the third day. In this patient a complete block on lumbar tap was present prior to reduction, but only a partial block afterward.

I have never seen recovery in a case of complete transverse lesion of the cord in the cervical region due to trauma. I question strongly the propriety of immediate operative intervention in such cases as it seems to me a waste of time and material, to say nothing of the distress that it may cause to the patient. In my experience, if the cord has been sufficiently injured in the cervical region to cause complete paralysis of the legs and sphincters, with marked motor involvement in the arms and loss of all forms of sensation below the level of the lesion, fatality has always resulted, no matter whether operative or nonoperative treatment was employed.

A Group of Tumors of the Spinal Cord. Dr. J. C. Yaskin, Dr. Bernard J. Alpers and Dr. C. A. Patten.

The diagnosis of tumors of the spinal cord is often difficult; that is especially true in early cases and in extramedullary tumors. The difficulties arise from the inability to obtain a satisfactory and accurate history, which is often confusing and misleading. During the past few years the use of iodized rape seed oil has considerably aided the making of early diagnoses. Tumors of the spinal cord present less difficulty when, by their growth, they cause serious involvement of the cord; but at that stage the therapeutic possibilities are less favorable. Therefore, the goal is an early diagnosis and early surgical intervention. Some of these facts were impressed on us by the management of four cases observed during the past few months.

Case 1.—*Pain in the right leg for two years; pain on the opposite side, and paralysis of both lower extremities and of sphincter control for a few months. At operation, an extramedullary fibroblastoma was found at the level of the first and second dorsal vertebrae.*

History.—M. B., aged 59, a housewife, was admitted to the Graduate Hospital (service of Dr. T. H. Weisenburg) on Nov. 23, 1931, complaining of pain and paraplegia in both lower limbs. The family history was irrelevant, with the exception of an attack of smallpox in 1907. The past medical history was likewise without significance. In the early part of the winter, 1929, the patient noticed a soggy sensation in the toes of the right foot; she stated that it felt as though "it were in water all the time." When bathing, the foot felt considerably hotter than the rest of the body. Pain developed a few months later; it was first present in the toes of the right foot. The patient went to a hospital in August, 1930, but obtained no relief. At about that time the entire left lower extremity became painful; lastly, the pain was felt in the right leg and thigh. Once the pain started in a certain locality it remained there constantly, though she experienced severe exacerbations. The pain gradually extended to other regions, until there was pain almost to the level of the costal margin on both sides. During the course of the day, from time to time, she experienced severe seizures of a superimposed pain which started in the toes as a burning sensation, changed to a clawing, gripping sensation and slowly ascended to the waist. Filling of the bladder aggravated the condition considerably. Trouble with the bladder started in October, 1931, while the patient was in the Orthopedic Hospital, where for the first time she had to be catheterized. When she left that hospital and remained home for a few days she voided spontaneously when she was held in the sitting posture. A few weeks prior to the writing of this paper, while she was having a bowel movement, she was unable to tell whether or not feces were passing. She had never had incontinence of the rectal or vesical sphincters. Early in the winter, 1930, the left foot began to drag, and she began to use a cane. In the latter part of July, 1931, she began to lose power in the right lower extremity. In a short while she lost power in both lower limbs.

Examination.—The patient was rather stout, and was completely bedridden, owing to paralysis of both lower extremities. General physical examination gave essentially negative results, except for rather poor heart sounds. The blood pressure was 158 systolic and 72 diastolic.

Neurologic Examination: The cranial nerves and upper extremities were normal. The biceps and triceps jerks were bilaterally active and equal. The patient was unable to sit up without aid, owing to weakness in both abdominal muscles and iliopsoas muscles. The abdominal reflexes were not obtained. The lower extremities lay limp and motionless. No fibrillary tremors were visible. Occasionally, on pinching, some movement was elicited (reactions of defense). The patellar and ankle jerks were bilaterally increased, and there was a bilateral Babinski sign.

The temperature was not correctly interpreted up to the level of the seventh dorsal vertebra posteriorly and the costal margin anteriorly. There were scattered areas of intact sensation to pain at the left knee and on the external part of the left thigh about the level of the pelvis, but it was not definitely recognized until the level previously mentioned was reached. Light touch revealed the same manifestation, but there was an intact area in the suprapubic region. Sensation of passive motion was lost in the big toes of both feet. The patient did not recognize vibration in either lower extremity.

Pelvic examination gave negative results except for laceration and relaxation of the perineum. Roentgen examination showed a slight increase in density in each hilus, and there were no evidences of metastatic involvement of the lungs. Examination of the dorsolumbar spine showed a slight dorsal lumbar kyphosis, with a slight left lumbar scoliosis; there were no evidences of metastatic involvement.

All laboratory investigations, including urinalysis, chemical examination of the blood, blood count and Wassermann test of the blood, gave negative results. Lumbar puncture revealed a clear fluid at a pressure of 21 cm. of water, rising slowly with bilateral jugular compression to 30 cm. and failing to fall. After the withdrawal of about 10 cc. the fluid became blood-tinged. Chemical and cytologic examinations of the fluid gave essentially negative results.

The advisability of making an injection of iodized rape seed oil was considered, but in view of the severe pains it was deemed best to expose the cord and if no tumor was found to do a bilateral chordotomy.

Operation (Dr. F. C. Grant, Nov. 7, 1931).—Amytal, avertin and procaine hydrochloride anesthesia were employed. The original incision was planned to extend from the second to the seventh thoracic vertebrae. The cord was exposed without difficulty in this region and no tumor was found, although the vessels of the back of the cord were tremendously engorged. This observation, coupled with the fact that no fluid was coming down from above, led to the removal of the first and second laminae. Palpation of the dura in the upper extremity of the wound revealed a hard tumor beneath it. The dura was opened carefully over the tumor, which lay altogether on the left side of the cord and anteroposterior to it. It was a flat encapsulated tumor lying probably outside the arachnoid. It was almost like a meningioma *en plaque* and had a large dural attachment. The tumor pressed the cord tightly. The dura around the base of the tumor was cut, and the tumor was slid out without difficulty. The attachments of the dura to the arachnoid over the cord were dissected away without bleeding. There was some bleeding from two small vessels above and below the tumor on the anterior aspect of the dura, which was checked with muscle graft. In the removal of the tumor it was necessary to section what were probably the first and second thoracic roots, both anterior and posterior, on the left side. After the removal of the tumor the cord swung well over into the midline and, though there was a definite depression in the cord at the point where the tumor had lain, there was no reason to believe that there was damage of the cord other than that which had already occurred owing to the presence of the tumor. Owing to the large dural defect it was impossible completely to close this membrane; it was closed from below up to about the fourth thoracic segment.

Postoperative Course.—Immediately after the operation the patient's condition was good, but on the following morning bilateral bronchopneumonia developed, and she died on Oct. 10, 1931.

Microscopic examination showed that the tumor was a fibroblastoma.

Comment.—Although in retrospect the history and chronological development of symptoms and signs made the diagnosis relatively clear, the condition was permitted to progress to a complete paraplegia before operative procedures were even considered. Had a tumor been suspected, an injection of iodized rape seed oil might have revealed the lesion months before the onset of paraplegia. Considering the location of the tumor, it is surprising that there was so much pain in the lower extremities. The edema and possibly other vascular changes might explain the occurrence of these pains at a much lower level. No explanation was found as to why a full bladder seriously aggravated the pains.

CASE 2.—*Root pains for three years; later, atrophy in the right upper extremity, and, more recently, slight pain and beginning atrophy of the left upper extremity. No definite evidence of involvement of the white tracts of the spinal cord or of spinal block. Injection of iodized rape seed oil inconclusive. At operation, dilatation of the vessels on the posterior surface of the cord, extending from the second to the eighth cervical vertebrae. Relief of symptoms.*

History.—J. O., aged 23, a tailor's helper, was admitted to the Graduate Hospital (service of Dr. T. H. Weisenburg) on Oct. 23, 1931, complaining of pain and weakness in the right hand. The family and past histories were irrelevant. Three years prior to presentation, the patient first began to have pain and a sensation of pins and needles in the right arm, which were most marked about the lateral epicondyle and radiated into the shoulder. With such attacks the arm felt stiff, especially during damp weather. About one year before presentation, the pain, which had been constant with paroxysms, had spread to the shoulder and to the right side of the chest at the level of about the fourth or fifth rib anteriorly and the midscapular region posteriorly. About three weeks ago, the left elbow became affected, and she now has pain in the left upper extremity. During the last two years, her weight has dropped from 115 (52.1 Kg.) to 94 pounds (42.6 Kg.). About eighteen months before this paper was written, she first noticed that the right hand and forearm were greatly shrunken and that the grasp was much weaker than normally. This was especially observed in the movements of the fingers. The patient's occupation requires the constant rotation of a small wheel with the right hand and the manipulation of a piece of cloth with the left hand. She has observed occasional twitching or tremors in the movements of the right forearm. No changes in sensation have been noted as to recognition of familiar objects and differentiation of heat and cold. In addition, in the past three months she had had continuous frontal headache and loss of appetite. In the last month there was twitchings of the right hand and forearm. There were no subjective symptoms referable to walking or to the lower extremities; there have been no disturbances in sphincter control. For the past three summers she has also been having fainting spells. There were no symptoms referable to any other system. She recalls no injury to the back and has never had dorsal pain.

Examination.—The patient was slender and normally developed. The general physical examination gave negative results. Pulse rate, temperature and blood pressure were within normal limits.

Neurologic Examination: The cranial nerves were normal. The upper extremities showed: Right arm: There was atrophy of the forearm and interossei muscles. The right forearm measured 12.5 cm.; the left 13.5. Both thenar and hypothenar eminences were definitely atrophic. The dynamometer reading was 30 (left, 60). There were definite weakness of the flexors and extensors of the hand and forearm, and some weakness of the pronators and supinators. There were flattening of the deltoid and wasting of the right shoulder and scapular regions. No tremors were visible, and the electrical reactions showed no evidences of degeneration. Left arm: There was flattening of the interossei and of the thenar and

hypothenar eminences. The biceps and triceps were preserved, and there was a doubtful Hoffman sign. Trunk: There was no disturbance in function; the abdominal reflexes were bilaterally preserved. Lower extremities: There was no weakness or atrophy; the knee and achilles jerks were bilaterally hyperactive; there was a sustained ankle clonus on the left and occasional fanning of the toes on plantar irritation of the left foot. Sensation: Repeated examinations revealed no objective disturbances anywhere in the body. There were no sphincter disturbances.

All laboratory investigations gave negative results. Lumbar puncture revealed a normal pressure and a free rise and fall on jugular compression; the color of the fluid was normal, and chemical and cytologic examinations gave negative results. Roentgen examination showed both the head and the vertebral column to be entirely normal.

Iodized rape seed oil was injected by the cisternal route on October 29. It traveled without obstruction the complete length of the spinal canal from the cisterna to the lower end. Films also revealed fuzziness in the outline of the body of the sixth cervical vertebra. Further examination of the cervical spine revealed irregular, mottled resorption of the right side of the posterior upper portion near the base of the lamina of the sixth cervical vertebra. Examination otherwise revealed nothing abnormal. It is impossible to ascribe a definite etiology to the changes in the cervical spine just described, but it is possible that they were the result of an underlying lesion of the cord, such as one might expect from pressure atrophy, or in some other way the result of interference with the blood supply to the osseous structures.

The diagnosis in the case remained obscure. The following possibilities were considered: an extramedullary tumor of the cord; hemangioma; early amyotrophic lateral sclerosis, and early syringomyelia. It was felt justifiable to perform an exploratory laminectomy.

Operation (Dr. F. C. Grant, Nov. 9, 1931).—Under amytal, avertin and procaine hydrochloride anesthesia, which required reenforcement with about ½ ounce (14 Gm.) of ether, a laminectomy was performed. There was no bleeding until the spinous processes of the laminae were removed. It was then seen that the extradural venous plexus was much engorged, particularly on the left side. The veins were so large that when they were first encountered an extradural tumor was suspected. There was difficulty with bleeding from the veins, but a satisfactory hemostasis was obtained. It is possible that these veins might be the cause of the difficulty, although when the blood supply had been cut off they collapsed, and the possibility that they were of sufficient size to cause the symptoms seemed rather remote.

The dura was then opened widely and the cervical segments, from the third to the eighth, were exposed. The cord was not enlarged in this region nor did it fill tightly the subdural space. Fluid came up freely from below, showing that there was no block above this point at the level of the foramen. The only abnormality that appeared was the slight dilatation of the arteries on the posterior surface of the cord. The dilatation seemed to begin roughly at the eighth cervical segment and to extend up to about the second. The anterior part of the canal was examined closely and nothing suggesting an anterior tumor was discovered. The anterior and posterior roots appeared normal, though they may have been a little larger than usual. There was no discoloration to suggest neuritis. A probe was passed below the eighth cervical segment for a distance of about 4 inches (10 cm.) anterior and posterior to the cord, and no obstruction was encountered.

Postoperative Course.—The patient made an uneventful recovery; at no time did paralysis of the limbs develop; the pain disappeared immediately after the operation, and she was discharged in good condition on Dec. 3, 1931.

Comment.—In this case, while no definite tumor mass was found, the patient nevertheless obtained relief and suffered no harm. Whether or not there were intramedullary changes that will manifest themselves by more definite symptoms

later or whether the vascular changes were responsible for all these changes can be decided only by the future.

CASE 3.—*Backache and later pain and weakness in both legs, attributed to injuries sustained three years previously. Radicular pains and atrophy in the right extremity but no other evidences of involvement of the spinal cord. After repeated lumbar punctures xanthochromic fluid was obtained, and studies made after the injection of iodized rape seed oil revealed a block at the twelfth dorsal vertebra. At operation, a perineural fibroblastoma was successfully removed, and the patient made a satisfactory recovery.*

History.—J. B., a man, aged 20, a mill worker, was admitted to the Graduate Hospital (service of Dr. T. H. Weisenburg) on Sept. 18, 1931, complaining of pain in the back and both legs. He had played football in the fall of 1928 and attributed the present illness to injuries received while playing. There was no definite history of any single injury that he could hold responsible for the difficulties. He first began to have pain about July, 1929, and at that time the pain was located over the left side of the chest and was made worse by coughing. The pain persisted for about two months, when pain developed in the lower part of the back. The patient was admitted to the Philadelphia General Hospital, where a cast was applied and retained for six weeks, but it afforded no relief. About that time pain developed in the right leg, which has persisted. The patient has been in several hospitals, without obtaining benefit. The pain is constant, dull, aching and worse at night. In addition to the pain there has been weakness, especially in the right thigh. There has been considerable loss of weight owing to the inability to sleep and rest. There have been no sphincter disturbances or symptoms referable to any other system. At times he received relief; thus he was admitted to the Orthopedic Hospital in January, 1931, and with rest, baking and massage showed considerable improvement. When he was discharged, however, the pain recurred. On July 13, tonsillectomy was performed, without relief. On September 18, he was readmitted to the Orthopedic Hospital for study with injection of iodized rape seed oil.

Examination.—A general physical examination revealed no evidence of visceral disease or of focal infection. The patient was pale and emaciated, being worn out by sleepless nights.

Neurologic examination showed no abnormalities of the cranial nerves or upper extremities. There was no weakness in the muscles of the trunk. The abdominal reflexes were bilaterally present and active. The cremasteric reflex was present on the left but absent on the right. There was definite weakness of both iliopsoas muscles and of both adductor and quadricep groups, more marked on the right than on the left. There was definite atrophy of the right lower extremity as compared with the left, the measurements of the lower part of the thigh on the right being 11 inches (27.9 cm.), on the left, 12½ inches (31.6 cm.); of the upper part of the thigh on the right side, 14 inches (35.4 cm.) and on the left, 15¼ inches (38 cm.). There was also weakness in extension of the right foot. No fibrillary tremors were noted, and no electrical reactions of degeneration were obtained. The left knee jerk was within normal limits; the right was distinctly diminished. The achilles jerk, on the other hand, was better marked on the right than on the left. There was a suggestion of a Babinski sign on the right, with normal flexion of the toes on plantar irritation on the left. While there was a great deal of subjective pain, there were no objective sensory disturbances in any part of the body. When he attempted to carry out the Lasègue sign, there was inability to extend the thighs without producing much pain.

Laboratory investigation revealed no definite abnormalities except for the spinal fluid and roentgen studies. The temperature and pulse were normal. Examination of the urine, chemical analysis of the blood, Wassermann test of the blood and blood count gave normal results except for a mild secondary anemia. Lumbar puncture, performed in January, 1931, revealed no abnormalities of pressure or of chemical or cytologic findings. A lumbar puncture performed on Sept. 1, 1931, revealed an initial pressure of 8 cm. of water, with a prompt rise and fall on

coughing and jugular compression, the impression being that there was no block. However, the fluid was slightly xanthochromic and showed spontaneous coagulation. The lumbar punctures made in other hospitals had revealed no abnormalities. Roentgenograms of the spine and chest gave entirely negative results.

On September 5, iodized rape seed oil was injected into the cisterna magna. Films made fifteen minutes after the injection showed that it had descended to the level of the upper border of the twelfth dorsal vertebra. In the lateral view it seemed as though the oil had infiltrated along the posterior roots. There seemed to be definite occlusion at this level. A film made eighteen hours after the injection showed no further downward movement of the oil. There was nothing distinctive in appearance, however, which might enable one to make a diagnosis of tumor of the cord.

Course in the Hospital and Operation.—The patient remained under observation until October 1, suffering a great deal of pain. After admission to the hospital, pain in the left as well as in the right leg developed. A diagnosis of tumor of the cord was made, though the history of the injury suggested that there was also a possibility of arachnoiditis.

A laminectomy (Dr. F. C. Grant, October, 1931) was performed under amytal, avertin and procaine hydrochloride anesthesia, which required reenforcement with a little ether. As soon as the laminae were removed, it was seen that the cord was compressed within the dura at the level shown by the injection of iodized rape seed oil. The dura was thin and the posterior root was slightly adherent to its under surface. The roots in this area were red and inflamed. At first the tumor could not be seen, but by separating the roots below the lower pole an encapsulated tumor lying in front of the cord was found.

The roots of the cauda were carefully separated over the posterior surface of the tumor, and it was then seen that the tumor extended upward under the cord itself. The tumor was rather more adherent on the right anteriorly, not being attached to the left side of the dura surrounding the cord. After careful manipulation the lower three quarters of the tumor was seen, but the upper pole was still hidden by the cord. The tumor was probably 4 cm. long and 2 cm. across, as large as the end of an adult thumb. An incision into the tumor was made with a Bovie knife, and it was found that it was not particularly vascular. Intracapsular removal with a curet was done, and when the tumor was sufficiently reduced in size it was freed from the upper pole without too much pressure on the cord. After manipulation and dissection the tumor was dislocated from its bed. However, in this position the bulk of the tumor lay between the operator and its attachments to the dura, so that the bulk of the tumor was removed with the Bovie knife. After this had been done, the part of the tumor attached to the dural wall was removed. Owing to the closeness with which the roots of the cauda equina surrounded the point of attachment, and owing to the fact that this lay anterolaterally, the part of the dura from which the tumor sprang was not removed. This makes a recurrence possible.

Postoperative Course.—Inability to urinate followed for a few days without loss of sensibility of the bladder. Immediately after the operation the patient lost power in the right leg, but he regained it in a few days. There was also a transitory sensory disturbance. When discharged on October 19, he was in good condition and fully able to walk around. When examined on December 15, he had no sphincter disturbances and was able to walk without much difficulty. The right thigh measured 29 cm. and the left, 35; the right leg measured 28.5 cm., the left, 29 cm. The right knee jerk was barely obtainable; the left was normal; the right achilles jerk was absent, and the left was normal. There were no sensory disturbances in any part of the body; the patient was entirely free from pain.

Microscopic Report of Tumor.—A diagnosis of perineural fibroblastoma was made.

Comment.—A relatively early diagnosis was made possible by repeated lumbar punctures and the use of iodized rape seed oil. The treatment for neuritis, if continued much longer, would undoubtedly have resulted in irreparable damage of the cord.

CASE 4.—*Severe trauma followed by pain in the back, and later by persistent pain in the left leg. Weakness of the left leg. Absence of achilles reflex on the left. Vague sensory findings up to eighth thoracic vertebra on the left. Injection of iodized rape seed oil and arrest of iodized oil at third lumbar vertebra. At operation a small extradural tumor compressing the roots of the cauda equina on left. Histologically, a chondroma. Complete recovery.*

History.—E. F., a woman, aged 49, entered the Graduate Hospital of the University of Pennsylvania in April, 1931, on the service of Dr. William Bates. Three years previously she had slipped and fallen, striking violently on the buttocks. Several hours later she had pain in the small of the back; pain in the left leg began about one year after the fall. The pain in the leg, at first intermittent, later became almost constant; it was paroxysmal, beginning in the region of the left hip and radiating down the back of the thigh into the leg; often it was so severe that it was necessary for the patient to assume the knee-chest position in order to obtain relief. Shortly after the development of pain she noticed weakness in the left leg, and at the time of entrance into the hospital the patient was unable to walk without a limp. The right leg was singularly free from pain throughout the course of the illness. Within recent weeks she had noticed numbness of the left leg.

Examination.—No cause of a surgical or orthopedic nature to explain the pain was found. Neurologic examination revealed a weakness of the left leg involving the muscles of the thigh, leg and foot. Movement of the left leg caused pain. On the left side, extending from the sole to the level of the eighth thoracic vertebra there was decreased sensation to touch, pinprick, heat and cold. The achilles reflex was absent on the left; it was active on the right, and both patellar and arm reflexes were active and equal. The abdominal reflexes were absent bilaterally. There was a positive Lasègue sign on the left. Repeated examinations confirmed the sensory findings already noted; while slight, they were nevertheless distinct. It was thought that the patient had a lesion of the cauda equina which was probably extradural and chiefly on the left side, but that there was also another lesion, probably at the level of the eighth thoracic vertebra.

A lumbar puncture was made, and no subarachnoid block was demonstrated. The routine tests gave negative results. Because of the indefiniteness of the clinical signs and the long duration of the illness — three years — with relatively few clinical manifestations, an injection of iodized rape seed oil was made. A roentgenogram taken after this injection showed that the iodized oil had stopped opposite the body of the third lumbar vertebra. In spite of all efforts to displace it, the oil remained steadfastly in this situation. Therefore, another lumbar puncture was made, between the fourth and fifth lumbar vertebrae, and with the needle in this position it was found that a block could be demonstrated. Furthermore, the spinal fluid removed from this locus had a xanthochromic appearance. Roentgen examination of the dorsal and lumbar spine revealed an old hypertrophic osteo-arthritis, but nothing else of significance.

In view of the observations made after the injection of iodized rape seed oil and the demonstration of a subarachnoid block, operation was thought to be indicated.

Operation.—On May 18, Dr. Grant performed a laminectomy, removing the third, fourth and fifth lumbar and first and second sacral spines and laminae. At the lower end of the cord the dura was dark and seemed to be markedly swollen. The dark and swollen region contained nothing but xanthochromic cerebrospinal fluid. Just above this area, impinging on the cord from in front, pushing up the dura and compressing the nerve roots, was a whitish mass. This was extradural and anterior to the cord. It seemed to involve the nerve roots

emerging from the level of the third lumbar vertebra. The cauda equina roots were retracted and an incision was made into the protruding mass, which seemed to arise from a point beneath the transverse processes of the third and fourth lumbar vertebrae. The contents were removed with a curet. They seemed to be cartilaginous. The mass was firmly anchored and arose from the intervertebral disk.

Course.—Postoperative pneumonia developed from which the patient recovered. The pain in the leg disappeared entirely, and all neurologic symptoms disappeared. The achilles reflex remained absent on the left side for some time.

DISCUSSION

DR. CHARLES H. FRAZIER: This series of tumors of the spinal cord has many points of interest to both the surgeon and the neurologist. I shall confine my comments, however, to pain as a factor in the diagnosis of tumors of the spinal cord and in their localization. I have always attached great importance to pain in both these connections. Pain is often the first symptom of tumors of the spinal cord, and is always the first symptom when, as in so many cases, the tumor, usually a fibroblastoma, takes its origin from the reflection of the arachnoid over the posterior root at its point of exit from the canal. The facts that the majority of tumors of the cord are fibroblastomas or fibromas and the large majority posterolateral rather than anterolateral substantiate the statements I have so often made as to pain.

Especially important in the diagnosis, as well as in the localization, is the fact that pain is referred to a given zone at the beginning of the illness (being a root pain) and continues in that zone throughout. Later, other roots may be involved and the pain be more widespread, but from the distribution of the first root involved the pain never disappears. Persistent and severe pain referred to a given point for a considerable time, not otherwise explained, should always arouse suspicion.

The case to which I am about to refer is illustrative. The patient, 31 years of age, complained of pain in the lower part of the back from the ribs down, which had been present for a year. Only eight weeks ago did other symptoms supervene. For example, there were weakness and stiffness in the right leg and a sensation of numbness in the calf of the right leg which rapidly progressed to involve the entire right leg. The weakness progressed and for six weeks past the patient has dragged the right foot when walking. There is also slight weakness of the left leg. During the past week there has been a sensation of a band drawn tightly around the right hip in the region of the groin. However, there was no loss of objective sensation, and there was nothing to determine the segmental level. On the persistent pain in a definite zone, not otherwise accounted for, I assumed a diagnosis of a spinal tumor and determined the level. Later, the provisional diagnosis and localization were confirmed. At the operation I exposed an enchondroma at the level of the tenth thoracic vertebra, about the size of a chestnut, probably taking its origin from the underlying intervertebral disk. The tumor was extradural and was exposed only after a transdural incision. It was readily removed, and convalescence was uneventful.

DR. N. W. WINKELMAN: Dr. Yaskin's statement about having to keep in mind the fact that tumors of the spinal cord may progress so slowly that unless one is on guard they may easily be overlooked is true. This brings up a medicolegal problem that we have recently had in two cases in which tumors of the spinal cord were suspected but could not be definitely proved until twenty-four hours after a Queckenstedt test, when a complete and total paralysis of both lower limbs developed. This patient might easily have had cause for legal action, and now we usually warn patients and families of this possibility. A patient with such a condition has recently come to autopsy at the Philadelphia Hospital, and the process proved to be an intramedullary glioma.

DR. WILLIAM G. SPILLER: The difficulties in diagnosing tumors of the spinal cord sometimes call for detective ability. I recall a patient whom I saw in consultation with Dr. Strecker at the Jefferson Hospital. I made a diagnosis of a tumor in the upper thoracic region. The patient was placed under the care of Dr. Frazier for operation. She was a heavy woman and was completely paralyzed in both lower limbs. While she was in the University Hospital sensory disturbances in the distal portions of the upper limbs developed, and it was supposed by some who saw her that the lesion was in the cervical cord. It occurred to me that in adjusting herself in bed she probably raised the paralyzed lower part of the body by supporting herself on her elbows, and in this way caused pressure on the ulnar nerves, with resulting disturbance of sensation in the distribution of these nerves. The diagnosis of tumor in the upper thoracic region below the origin of the brachial plexus was found at operation to be correct.

DR. B. J. ALPERS: I wish to call attention to the fact that, in the last case particularly, the symptoms of sciatica were entirely unilateral. One is so often reminded that bilateral sciatic pain is suggestive of tumor that one forgets that unilateral pain in this distribution may be due to a tumor. It was true in two of the cases reported. In the last one in particular, the pain was entirely unilateral, an observation that tended to confuse the clinical picture when I first saw the patient. I wish to call attention, too, to the pain in the back which this fourth patient presented. It is a fairly frequent symptom of tumor of the cauda equina, a fact first pointed out by Dr. Spiller many years ago.

DR. FRANCIS C. GRANT: My purpose is to reiterate and emphasize various statements that Dr. Yaskin has made. The pain of which the woman in case 1 complained was the most severe I have ever observed accompanying a tumor of the cord. Furthermore, the pain was referred to the feet and legs and to the bladder when it became overdistended. The pain was so intense that we were prepared to perform a bilateral chordotomy for its relief if no tumor was found. I cannot recall a case of tumor of the cord in which there was pain of sufficient severity to require 4 grains (0.26 Gm.) of morphine a day for its relief, or of such a character that shaking the patient's bed would precipitate a paroxysm. From her age and the wide distribution of the symptoms, multiple metastatic lesions were believed to be present, although all examinations, including complete roentgen studies, failed to reveal a primary focus. That a single large anterolaterally placed meningioma at the level of the fourth or fifth thoracic segment could have caused such intense bilateral pain in the legs is unusual. However, it is possible that she may have had a second similar lesion at a lower level, although multiple meningiomas of the cord are far from common. In any event, the removal of the one growth completely relieved the pain during the seventy-two hours during which she survived the operation.

I am far from certain that the patient in case 2 had a tumor. When the spines and laminae were removed, the epidural fat was thick and purple instead of the usual yellowish hue. I expected to find a solid extradural tumor. On the contrary, after clipping one or two bleeding points and two rather large veins that ran into this purplish mass, it collapsed and lost its curious color. I excised as much of this material as possible, finding the dura below the mass entirely normal in appearance. There was no tumor within the dura about the cord or other abnormality of the cord itself to explain the symptoms. Microscopic study of the vascular tissue removed showed many thin-walled venous channels, suggesting a telangiectasis. A brief review of the literature shows that such tumors in this region are extremely rare. The patient was seen two months after the operation and seemed slightly improved. It is possible, of course, that the decompressive laminectomy can account for the improvement in her condition, and that later evidence of intrinsic disease of the cord may develop.

The last two cases demonstrate vividly the value of iodized rape seed oil in localizing lesions situated low in the cord below the level at which a lumbar puncture is usually made. Neither of these patients showed a block to lumbar puncture in the second lumbar interspace, and, curiously enough, the protein con-

tent of the fluid was not increased. It was only from the arrest of the iodized rape seed oil that the presence of the lesion and its level could be accurately determined. The case was particularly interesting because of the type of lesion present and its connection with the history of trauma. The patient was a farmer's wife and was carrying two pails of milk supported by a yoke across her shoulders. She slipped and sat down, striking solidly on both buttocks. The result was that the intervertebral disk was crushed and forced posteriorly, impinging on the cord. A recent follow-up letter reports much improvement in her condition.

DR. JOSEPH C. YASKIN: Apropos of Dr. Winkelman's remarks, it may be interesting to note that in a case of extradural spinal abscess in which there was no paralysis or spinal block, paraplegia and almost complete spinal block developed twenty-four hours after the spinal puncture. It appeared as if the lumbar puncture precipitated both conditions.

REMOVAL OF THE RIGHT CEREBRAL HEMISPHERE FOR INFILTRATING GLIOMA. DR. W. JAMES GARDNER, Cleveland.

A woman, aged 31, had been subject to convulsive seizures for about ten years. For several months there had been symptoms of increased intracranial pressure. On neurologic examination there were unmistakable signs indicating a tumor of the right parietotemporal region. At operation on Aug. 31, 1931, a large cauliflower-like infiltrating glioma was exposed in this region. The entire cerebral hemisphere, with the exception of the basal ganglia and small portions of the cingulate and uncinate gyri, was removed. The patient's convalescence was gratifying. Three months after operation she was able to walk with a cane and had some return of voluntary movement in the left leg. The left arm was completely paralyzed, and there was loss of sense of position and stereognostic perception. Light tactile and painful stimuli were not perceived, and heavier stimuli were not accurately localized on the entire left side. There was only a moderate asymmetry of the face. There was no demonstrable intellectual impairment.

DISCUSSION

DR. J. HENDRIE LLOYD: This is such an extraordinary example of operation on the brain, and so out of my range of observation that I hesitate to discuss it, except to refer to some physiologic questions which it seems to raise. This patient, as shown in the moving pictures, does not appear to be totally paralyzed on the opposite side. She moves her leg and even bears her weight on it, although, of course, the movements are feeble. The picture does not show the arm in motion, but it looks as though there might be some power left in it. I regret that the movements of the muscles of the face, tongue and orbit are not displayed more fully in the pictures. I should have liked to see how the patient used her muscles in smiling, whistling, showing her teeth, projecting her tongue, closing her eyes and moving the eyes. As I looked at the pictures I thought of a recent paper on decerebrate rigidity, as seen in cats, after transverse sections of the brain stem. Some power, especially coordination, seems to be located in centers lower than the cerebral hemispheres, just as it is in fishes and birds. In the former there is no cortex of the brain, and in the latter not much. There must be some such power left in man in the striate, thalamic and subthalamic regions.

DR. WILLIAM G. SPILLER: Dr. Gardner has repeated the operation first performed by Dr. Dandy. The condition in his patient is similar to that we have seen many times in hemiplegia from an extensive lesion of the right cerebral hemisphere. It is a well known law that in the human body the muscles on the two sides of the body which are usually innervated synchronously are bilaterally represented in the cerebral cortex. The muscles of the soft palate or the larynx are not paralyzed by a unilateral lesion. The ipsolateral innervation is accomplished through the uncrossed fibers of the pyramidal tract in the lateral column of the spinal cord.

In Dr. Gardner's patient walking is possible because the thigh muscles of each side are employed together in standing and walking, but the foot is employed in more isolated movements, as often one foot is moved without the other; therefore, in this patient the muscles of the left foot are more paralyzed. The upper limb, especially the hand, is frequently employed in isolated movements; therefore, this patient shows little return of function in the upper limb. The moderate paralysis of the left side of the lower part of the face may be explained in the same manner. It is interesting that mentality has been little impaired by the removal of the entire right frontal lobe, and yet I believe that careful psychologic tests would show a deficiency.

DR. W. JAMES GARDNER: I am chagrined to have called to my attention a point that I intended to make in introducing this paper. I claim no originality for this procedure. In 1928, Dandy reported on five cases in which a similar operation was performed. In the case that I have reported, the only part of the cerebral cortex remaining on the right side is a small portion of the cingulate and uncinate gyri.

A CASE OF POLYCYTHEMIA VERA WITH CEREBRAL SYMPTOMS. DR. A. M. ORNSTEEN.

A man, 40 years of age, married, a machinist by trade, was well until September, 1931. At the age of 15 years he had scarlet fever and pleurisy. In the past year he has lost considerable weight, and in May, 1931, he had his tonsils removed. He has been under a severe mental strain for the past three or four years because his wife has epilepsy. Her spells have been mostly nocturnal, and he has had little sleep on account of her condition.

At the onset of his present condition, in September, he experienced numbness in the three lesser fingers of the right hand extending up the ulnar half of the hand and forearm to the elbow. The symptom had not been sensed in the forefinger, thumb or outer portion of the hand and arm. The paresthesia has been accompanied by some loss of power in the right hand. The symptom has persisted to date, and has been associated with pain in the left temporal region. About the middle of November he felt a moderate amount of dizziness and saw spots before his eyes. On November 22, about 4 o'clock in the afternoon he suddenly experienced difficulty in speech. At first, he hesitated over an occasional word and was able to complete his sentences after he passed this "block." He then found it increasingly difficult to form sentences, until he was able to speak only in single words. He had no difficulty, however, in swearing; as Dr. Waggoner, the resident, put it: "He has been able to swear at all times." He has been unable to read aloud, but he says that printed matter is intelligible to him. He is unable to write or sign his name. On November 22, a physician found that the sight of the left eye was markedly impaired.

Examination made on December 2 showed that the patient tires mentally easily. He reads aloud from a magazine but stops frequently and will not continue unless urged to do so, because, he said, "I get too mixed up." He reads a half dozen words or so without much hesitation but with an occasional error in pronunciation. He occasionally misnames single letters as he reads them but is usually able to correct his errors. There is a tendency in reading to omit an occasional word entirely. He apparently does not readily understand what he reads, whether aloud or silently. His understanding of single words or of sentences is relatively superior to his ability to understand printed directions and to follow them.

He has great difficulty in writing. At the beginning of the condition he could not write his name. Now he can write it, as well as the name of his home town. He can write a few dictated words correctly. His other attempts to write words are characterized first by a tendency to perseverate, to continue with the initial letter or the general form of the previous word; secondly, by frequent gross differences between the dictated word and his version, as for instance "fande"

for "glad" and "feli" for "file," and thirdly, by a tendency to scribble after the first letter or two so that the remainder of the word cannot be distinguished. There is an interesting and great difference between the words the patient can spell aloud and the words that he can write. His inability to write is by no means caused by difficulty in spelling. He spelled "necessary," for instance, and "information," though he failed on some simpler words. Further, in attempting to write a word he almost always spells it aloud first, but this does not enable him to write it correctly. He has about as much difficulty in picking out wooden block letters to form a word as he has in writing the word. As in writing, he may say the correct letter and choose the wrong one, and he may go over this letter again and again when it is placed in his word and not reject it, apparently not recognizing that it is not the letter he is calling out. He seems to have as much difficulty in writing the name of an object he sees as in writing to dictation. He may spell the name correctly aloud as he writes it wrongly. He copies from print to script but only with many errors. To copy a word correctly seems to require great care and the exact matching of letter for letter. Few words are copied correctly.

Spontaneous speech is not extensive and is somewhat fragmentary, but he does not now seem to make any errors. He can repeat well single sounds and sentences of about twenty syllables; he does not hesitate and his inflection is normal. He can name common objects readily and he can even get such a special name as "stop-watch." He counts easily and correctly, and he can say the alphabet if he says it rapidly and if he is started by the letter A. He cannot arrange a series of wooden block letters in alphabetical order, although he can place the majority of them in correct sequence except for eight or ten omissions. He can say over the names and days of the week quickly, but he could not at first name the months of the year.

His understanding of spoken language is superior to his understanding of printed material of equivalent difficulty. He can understand simple questions and follow simple commands, but he becomes confused if he is given long directions or if they involve special exact orientation.

There is no disturbance in gait nor are there signs of local dysmetria or of apraxia in any form, except the ideomotor apraxia of agraphia. In the right hand there are hypalgesia and hypothermesthesia in the fifth finger, and in the fourth and third fingers and ulnar side of the palm and dorsum of the hand up to the wrist there is only hypalgesia. The recognition of two-point contact is greatly impaired in the area of hypalgesia but is normal on the index finger and thumb. The recognition of differences in weights is not grossly impaired in the fifth finger, neither is the sense of texture impaired. Stereognostic perception is affected on the ulnar half of the hand, but not on the radial side, so that he was unable to recognize a coin or a match in the affected area though he did in the ulnar side of the left hand. The right biceps and triceps reflexes are increased over the left; both knee jerks are greatly increased, but the right is somewhat sharper; a few clonic movements of the ankle are elicited on the right but none on the left, and the plantar reflexes are normal. There is no apparent facial weakness on the right side. There is some motor defect in the right hand grasp, the dynamometer reading on November 24 being right 65 and left 85. (He is right-handed.)

Examination of the eyes made by Dr. Fewell showed no ptosis or exophthalmos; ocular rotation, full, convergence good and no nystagmus. The pupils were unequal, the right being 4 mm. and left, 3 mm., and both reacted promptly to the usual reflexes. In the right fundus, the media were clear, the disk healthy and the margins slightly fuzzy but easily defined. The veins were dark, overfull and tortuous; no hemorrhages or exudates were seen. In the left fundus, the media were clear, the disk hyperemic and the nasal margins blurred. The veins were engorged, being almost three times the size of the arteries and quite tortuous. There were no hemorrhages or exudates. The visual fields charted by Wentworth showed a definite partial right homonymous hemianopia and enlargement of the blind spots.

A roentgenogram taken of the head as reported by Dr. Pendergrass showed that the pineal body was 12 mm. behind and 5 cm. above the arbitrary line without displacement. The pituitary fossa was within normal limits of size. The anteroposterior measurement was 10 mm., and the depth, 10 mm. There was some calcification of the petroclinoid ligaments. No evidence of increased intracranial pressure or of a localized lesion was found.

Dr. Fitzhugh reported: This is a typical case of polycythemia vera. The spleen is slightly enlarged (two fingerbreadths) below the left costal margin. There is cyanosis of the finger-nails, and the general color is moderately red-cyanosed.

Examination of the heart and lungs gave negative results.

Nine blood counts gave results varying between the following limits: red cells, 7,800,000 to 8,900,000; hemoglobin, 120 to 130; leukocytes, 13,000 to 18,700; neutrophils, 77 to 88; lymphocytes, 9 to 15; large mononuclears, 2 to 5; transitionals, none; eosinophils, 1 to 3, and nucleated red cells, none. The blood volume index was 1.13; the basal metabolic rate, plus 4 per cent; the direct van den Bergh reaction was delayed; the result of the indirect test was 0.6 units. The Wassermann reaction of the blood was negative. Urinalysis showed a specific gravity of 1.022, a faint trace of albumin and many hyaline casts. The blood pressure was 140 systolic and 100 diastolic.

FAMILIAL SCAPULOPERONEAL AMYOTROPHY. DR. HAROLD D. PALMER.

The series of cases that I wish to present as scapuloperoneal amyotrophy first came to my notice in June, 1930, at the Pennsylvania Hospital, department for mental and nervous diseases. A woman, aged 33, was admitted because of the sudden exacerbation of a mental disturbance of several years' duration. During the routine investigation it was discovered that she also suffered from an atypical form of progressive muscular dystrophy. Her father visited her frequently, and it was noted that he had a similar type of disease. He submitted himself for examination and was able to give a surprisingly accurate family history. Through him it was learned that throughout many generations a neuromuscular disease had been transmitted. Certain constant features were recognized by the informant as well as his ancestors, and the condition was accepted by each generation as a hereditary form of "neuritis or rheumatism." Males and females seem to be equally involved, no generations are spared, and the disease was passed through a second marriage (in the second generation) to two separate lines. The condition is traceable with accuracy through four generations, and it is said to have been present in more. Eight members of a family of twenty-two were affected. The fifth generation has not yet arrived at the homochronic level.

The most remote of these eight cases (date of onset estimated at 1800) occurred in a woman in whom slow, progressive wasting in the forearms, hands, feet and legs developed at about the age of 22 years. The informant, her grandson, stated that she walked with a peculiar gait, used a cane and had pronounced wasting in the extremities and shoulders. She died in the late seventies of pneumonia. The informant is quite certain that this woman suffered no incapacitation from the muscular involvement. In the informant's mother the same type of wasting in the extremities had developed, which progressed to the age of 33, when she was lost at sea. The onset occurred before the age of 26, and up to the time of her death she suffered no disability. From the description given, the gait was steppage in type, and neuritic pains were present. The informant was 64 years old, and was in normal vigorous health up to the age of 22. At that time he was employed as a clerk in the offices of the Pennsylvania Railroad and noted that his thumbs were weak, and that writing became difficult. The weakness progressed, and wasting appeared in the muscles of the hands and forearms. At 25 what he called "weak ankles" developed, and he noticed that he dragged his toes in walking. Atrophy of the muscles of the leg followed relatively soon, and at the age of 30 it was necessary for him to use a cane in walking. The progress

ceased in the early thirties, and he stated that the degree of atrophy existing at that time was essentially the same as that which he presented on examination in the summer of 1930, at the age of 64. The striking point is that he was able to continue in his occupation as a clerk, and that he developed and retained skill as a typist. The remission has been of about thirty-two years' duration.

Examination reveals a steppage gait and the feet placed rather wide; a cane is necessary to maintain balance. There is pronounced wasting in the peroneal group of muscles and bilateral footdrop with an appearance of talipes equinus. The muscles of the thigh are only slightly affected. The hands show marked atrophy, and wasting of the intrinsic muscles is extreme. The hand is the typical "griffin claw." The forearms are atrophic, the muscles of the arm are only moderately affected, and the scapular group show advanced atrophy. In a brother of the informant a similar disease developed at the age of 24, which progressed rapidly to the age of 32 or 33. He was lost at sea in the late thirties, and at the time of his death was working regularly as a seaman. A half-brother

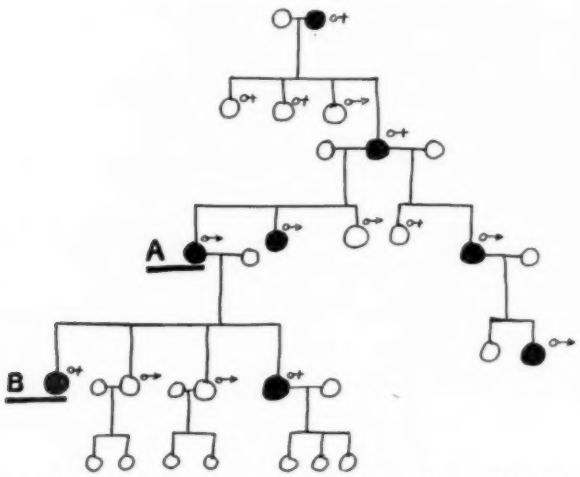

Fig. 1.—Familial scapuloperoneal amyotrophy. The afflicted members are indicated in solid black.

of the informant at the age of 36 presented a condition almost identical with that of the informant and the patient under consideration. He pursued his regular occupation as a merchant up to the time of his death at the age of 60 in 1929 due to a malignant condition of the prostate. A son of the informant's half-brother, aged 34, has the same disease, which at the time of this report is well advanced. He is employed as a salesman, and apparently suffers little inconvenience from the neurologic condition. The onset occurred in the early twenties, and the course has been from eight to ten years in duration.

The patient, a daughter of the informant, whom we had an opportunity to study in more detail was admitted to the Pennsylvania Hospital on June 28, 1930, because of an acute mental illness associated with toxic-infectious symptoms. Neurologic examination showed wasting of the hands, atrophy of the forearm and fairly well advanced wasting of the scapular group of muscles. There were weakness of prehension, adduction of the thumbs and flexion and extension of the wrists. Fibrillary twitchings appeared in the muscles of the forearm and scapular region. The lower extremities showed atrophy of the peroneal group with bilateral footdrop and talipes equinus position. Fibrillary twitchings were present in the muscles of the legs and thighs. The patellar reflexes were diminished, and the achilles reflex was absent. Reactions of degeneration were present in the peroneal,

forearm and scapular groups. The history agrees in its essential points with the course of the cases previously mentioned. The onset occurred at about the age of 25, and the course was comparatively rapid up to the time of admission at the age of 33.

Several additional features were mentioned by the informant as being typical in his own case and in those of his ancestors who suffered from the condition. Neuritic, lancinating pains were present, which persisted after the remission had made its appearance. The pain and paresis in the extremities were increased on exposure to cold. A sister of the patient, aged 39, has a more pronounced atrophy of the same anatomic distribution, and the onset is said to have occurred between the ages of 20 and 22 years. Identical features are present, and remission has apparently begun.

A number of features of the group under consideration seem to exclude it from classification, as Charcot, Marie, Tooth dystrophy, namely, the late age of onset,

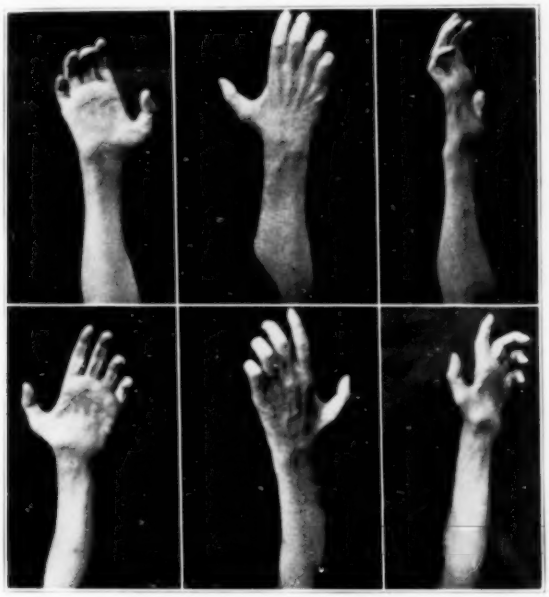

Fig. 2.—Hands and forearms of a man, aged 63 (third generation), showing advanced atrophic changes in the musculature of the forearms, the intrinsic muscles of the hands and the typical "main en griffe."

consistently prolonged remissions, the pain and paroxysmal paresis on exposure to cold and the prominent scapular involvement. The limited clinical criteria set up in the original papers of Charcot, Marie and Tooth (1886) have forced a considerable number of atypical variations of muscular dystrophy into the literature as new entities, or have made necessary the inclusion in this classification of forms not adequately fulfilling the specific criteria. This circumstance is similar to the case of Little's disease in which the term meant to apply to the fairly limited clinical syndrome originally described by that author has been expanded to include almost every type of infantile cerebral palsy. Davidenkoff (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **122**:628, 1929) described a familial scapuloperoneal amyotrophy closely resembling a clinical syndrome originally noted by Eisenlohr in 1889. The departures in localization of the atrophy in many respects resemble those of the series of cases we have been considering. In Davidenkoff's family of thirty-eight members, twenty-five were diseased, while only thirteen were

normal; no generation was spared; the hands, shoulder girdle and peroneal regions were chiefly involved; the age of onset was later than in the Charcot, Marie, Tooth variety; pain in the extremities was a prominent part of the clinical picture, and seven males and two females had prolonged remissions. This author (Davidenkoff: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **129**:244, 1930) would substitute the general term "neuro-spinal-muscular atrophy" in the place of the names of those authors which have been attached to the many, varied clinical types.

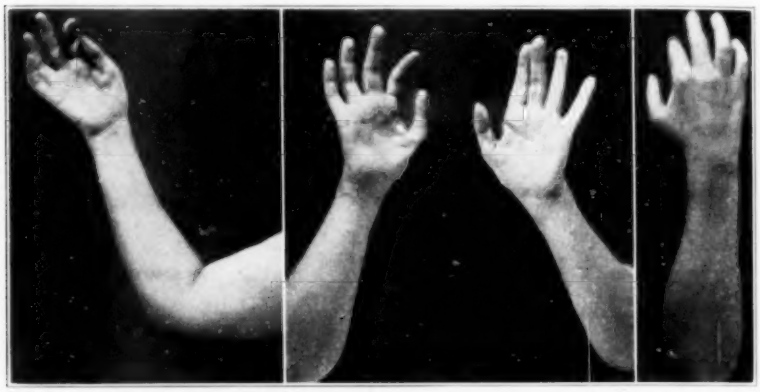

Fig. 3.—Hands of a woman, aged 33 (fourth generation). There are early but well defined atrophic changes in the musculature of the forearm, the interossei, and the thenar and hypothenar areas.

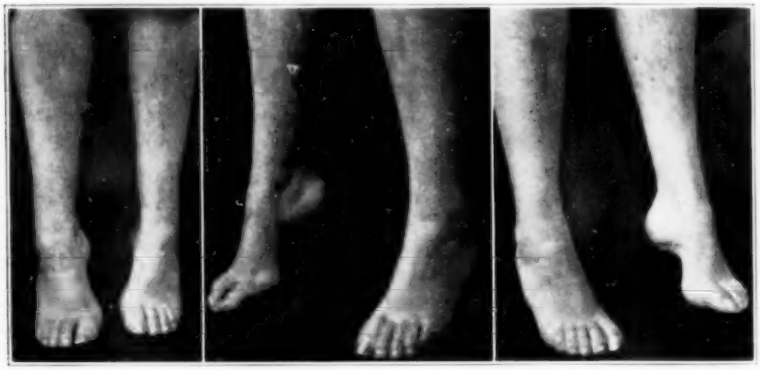

Fig. 4.—Legs and feet of the same patient as in figure 3 (fourth generation). Footdrop, pes cavus and early but well defined peroneal atrophy are present.

The prolonged course with lengthy remissions is not frequently encountered in the muscular dystrophies, though Spiller (*J. Nerv. & Ment. Dis.* **34**:15, 1907) described one case of forty-five years' duration and Eisenbud and Grossman (ARCH. NEUROL. & PSYCHIAT. **18**:766 [Nov.] 1929) found one of fifty-three years' duration. The duration of one of our cases (in the third generation) has been forty-two years, thirty-two of which fall in the period of the remission.

The complication of the picture by psychosis is mentioned only rarely in the literature. Siemmerling (*Arch. f. Psychiat.* **31**:105, 1899) had a patient in whom the dystrophy was associated with involutional melancholia. Raith (*Arch. f.*

Psychiat. **78**:28, 1926) described a case of schizophrenia in which a hereditary muscular atrophy seemed to have some etiologic relationship. Cavanaugh and Tucker (*New Orleans M. & S. J.* **81**:290, 1928) have written of the association of progressive muscular dystrophy with pronounced mental symptoms occurring in two brothers. They imply a relationship between the mental symptoms and the neurologic condition. Lelong and Courtios (*Bull. Soc. clin. de méd. ment.* **16**:38, 1927) described a case of progressive muscular atrophy with psychotic symptoms, both conditions apparently dependent on cerebral concussion and hypertension. In the patient admitted to the Pennsylvania Hospital, the mental symptoms closely resembled schizophrenia, but toxic and infectious processes created confusional factors which obscured the picture. It is my feeling that the psychosis is distinctly independent of the muscular dystrophy. This belief is supported by a review of the past personality and prepsychotic history of the patient, in both of which there appears a strong schizoid trend.

The vasomotor and sensory phenomena do not usually form a part of the clinical picture of the dystrophies. In the original description by Charcot and Marie, a patient was mentioned who had suffered lancinating pains in the extremities. "Cold paresis" or an increase in the paralysis in the extremities due to cold has been described by Davidenkoff (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **107**:259, 1927) in a recent paper defining two new dominant variants of neuromuscular atrophy. One variant is characterized by cold paresis not only as an individual variant but as a characteristic of a particular familial form. In the cases described by this author there occur transitory paralyses or paroxysmal exacerbations of a permanent paresis of the hands and feet due to exposure to cold. Davidenkoff calls attention to the original description of "this cold paresis" by Eulenberg under the term "paramyotonia." In my series of cases, exacerbations of the paresis and pain followed exposure to cold or putting the hands in cold water. Excessive protective measures have always been necessary in cold weather.

An attempt to comprehend the numerous present classifications of the muscular dystrophies meets with little satisfaction. As in other clinical syndromes, classifications on a basis of purely clinical criteria are at best only conditional, and it is unlikely that any degree of permanence or accuracy will be arrived at until clinico-anatomico-pathologic findings are coordinated. Throughout the literature dealing with the dystrophies one finds numerous discoveries of "hitherto undescribed" forms, which often are but slight variations from long established clinical syndromes. The purpose of this contribution has not been to introduce a new entity into the group but to present the histories and findings in a family suffering from an interesting variety of amyotrophy. The occurrence of scapuloperoneal amyotrophy in eight members of four generations of a family of twenty-two seems of sufficient interest to warrant recording. There were, however, a number of additional features that command interest. These are: (1) the existence of a definite homochronic level (the onset being rather strictly confined to the early part of the third decade); (2) failure of the disease to produce disability in any one of the affected members; (3) the definite remissions occurring usually in the early half of the fourth decade and continuing until life is terminated by intercurrent infections; (4) the complication of the picture by pain and vasomotor phenomena, and (5) the complication of the neurologic picture in the fourth generation by the presence of a psychosis.

Book Reviews

Das retikulo-endotheliale System der Schizophrenen: Experimentell-klinische Untersuchungen zum Schizophrenieproblem. By Dr. F. Meyer. Price, 12 marks. Pp. 124. Berlin: S. Karger, 1931.

In adhering to Bumke's contention that both the somatic and the psychic symptoms of dementia praecox give the distinct impression of an organic or toxic disease, Meyer is firmly convinced that the only natural way of promoting progress in psychiatric research lies in following the progress of general medical, physiologic and biologic knowledge. The investigation of psychiatric problems must therefore be intimately connected with the attainments and methods of approach of the biologic sciences. In this respect, Meyer finds it surprising that the reticulo-endothelial system, which in the last ten years has been of general interest in the domain of physiopathology, has so far been totally ignored in the field of psychiatry. This system, as delimited by Aschoff, in the main includes the reticular stroma cells of the spleen and of the lymphatic nodes, the endothelium of the reticular blood and lymph sinuses and the migratory cells of the connective tissue. It would be characterized by the property of storing dyestuffs in their granular form and of taking up corpuscular blood elements and various substances. The reticulo-endothelial cells would take part in the metabolism of iron hemoglobin, cholesterol and proteins. Their ability to incorporate and disintegrate proteins and irritating elements accounts for the fact that the reticulo-endothelium is deemed to play a conspicuous rôle in the processes of prophylaxis and immunity of the organism. This assumed specific function has promoted various procedures in order to test the alteration of the normal activity of the reticulo-endothelial system in the course of an infectious disease. Moreover, attempts have been made to investigate whether the function of this system may be influenced in both the sense of an increase and that of a decrease. Two functional tests were used in this study: (1) the congo red test of Adler and Reimann, to determine the storing capacity of the reticulo-endothelium, (2) the methods of Kauffmann, supposed to test the defense reaction of the organism.

1. While the patient was fasting, from 5 to 10 cc. of venous blood was withdrawn, whereupon 12 cc. of a 1 per cent solution of congo red was injected intravenously. Four minutes after the injection, and again one hour after the injection, 5 cc. of venous blood was again obtained from the other arm. The blood must be centrifugated immediately after withdrawal from the vein. The determination of the concentration of the dyestuff in the two specimens of serum was made with the scalephotometer (Stufenphotometer) of Zeiss and is expressed by an index:

$$\frac{\text{Dye concentration of the 60 minute serum}}{\text{Dye concentration of the 4 minute serum}}$$

2. Kauffmann's test was carried out as follows: A cantharides plaster (2.5 cm. square) was applied in the external region of the leg below the knee. The plaster was removed after twenty-two hours, and the reaction was observed. The latter varied from a more or less pronounced erythema, without vesicular formation, to one or more vesicles of various sizes. The vesicular content, which varied from 1 to 1.8 cc., was collected in a graduated pipet and measured. The color and general aspect of the exudate were noted. Finally, the number of cells per cubic millimeter and the differential determination of the various types of cells were determined by the routine procedure of examination of the blood.

This study was carried out in cases of schizophrenia (sixty cases); dementia paralytica (twenty cases), epilepsy (twenty cases), imbecility (twenty cases), encephalitis (four cases) and manic-depressive psychosis (six cases).

The congo red test gave the following results: In patients with schizophrenia, the index was between 50 and 70 in five cases, between 70 and 80 in twenty-four cases, between 80 and 90 in nineteen cases and between 90 and 100 in twelve cases; in eight cases it was 100.

In patients with dementia paralytica, the index was below 70 in one case; between 70 and 80 in nine cases and between 80 and 90 in ten cases. The highest index was 88.

In patients with epilepsy, four showed an index under 70, eight indexes were between 70 and 80 and 5 between 80 and 90, and three gave an index over 90. In imbeciles, the index was found to be under 70 in eight cases, between 70 and 80 in ten cases and over 80 in two cases. The results obtained with Kauffmann's test do not lend themselves to summary.

The high indexes obtained with the congo red test in most cases of schizophrenia would be significant so far as they are supposed to demonstrate a decrease of the storing capacity of the reticulo-endothelial system. This hypofunction is ascribed by Meyer to the reticulo-endothelial cells being overloaded by certain substances that do not manifest their existence in periods free from psychotic symptoms. Although recognizing the fact that the origin and nature of these substances are unknown, he believes that his findings bring support to the theories of infection, of gastro-intestinal auto-intoxication and of toxicosis by products of protein disintegration. The observations made with Kauffmann's test not only would suggest that the reticulo-endothelial system is injured by toxic substances, which may thus be considered as causative agents of the psychic disorders, but would moreover demonstrate a lowering of the general defense reaction of the organism. This study leads Meyer to conclude that schizophrenic (mental) troubles express the struggle of an organism in which the immunity is lowered when in contact with a toxic agent, which at present remains undiscovered.

In attempting to evaluate these painstaking investigations, the reviewer thinks that the results obtained have been greatly overrated. The exact significance of the congo red test is far from established. The reticulo-endothelial elements are not the only ones capable of storing dyestuffs introduced into the general circulation. The high indexes might as well be attributed to hypofunction of the choroid plexuses (?). Nor are reasonably adequate data available to substantiate the virtues attributed to the Kauffmann test. The reviewer cannot but think that the work of Meyer would gain if it were recorded in a few pages as research material that has not sufficiently matured to suggest definite inferences.

Intracranial Tumours. By Harvey Cushing. Price, $5. Pp. 150. Springfield, Ill.: Charles C. Thomas, 1932.

This volume on intracranial tumors summarizes the work of Harvey Cushing. Thirty years ago, when Cushing began this work, the surgery of tumors of the brain was looked on with considerable dread. Now, no metropolitan center is without a competent brain surgeon. The case mortality is less than 10 per cent, while for certain types of tumors it is much less. Admittedly, surgery of the brain has progressed more in this country than in Europe. This has been a matter of general knowledge for many years. That its progress has been in large part due to Cushing was well shown in the recent International Neurological Congress in Bern, where the subject of this book was the basis of a paper read by him, and where he was acknowledged as the outstanding contributor to neurosurgery of his time.

This book of 150 pages merely outlines what he himself has done and the work of his clinic, to which direct reference is constantly made throughout the book. It is to be hoped that someone will gather together in one volume all of the important contributions that have come from this clinic, for in the years to come such a compilation will be of value.

This book gives only the surgical aspects of 2,000 verified cases of tumor of the brain, with the surgical mortality percentages pertaining thereto. The case subject divisions are in three categories: tumor suspects, tumors histologically unverified and tumors histologically verified. In the first group there are 1,031 patients, but the classification was begun only fifteen years ago. In many ways the tumor suspects are the most interesting, certainly from a diagnostic point of view. The histologically unverified group comprises 859 cases, while the histologically verified tumors number 2,023.

Of the last group, the gliomas comprise 862, or about 42.6 per cent; the next in frequency are the pituitary adenomas, numbering 360, or 17.8 per cent. Then come the meningiomas — 271, or 13.4 per cent. The gliomas are again divided into unclassified and classified. In the former there are 175, while of the latter

the astrocytomas are the most common. Perhaps nothing indicates more the progress of neurosurgery than the knowledge gained from the life history of these tumors and their operability. The neurosurgeon with the modern supravital method has an enormous advantage, for he can tell during the operation the nature of the tumor and is aided in his method of handling it by such knowledge. Cushing's statement that pituitary adenomas are probably as common as thyroid adenomas is striking.

Perhaps the most interesting chapter in the book is that on operative statistics in general. Herein are shown the mortality for the entire period of thirty years in the verified tumors of the four major groups, the mortality percentages year by year, and the mortality percentages for the separate groups of tumors. In the gliomas, for example, the mortality up to 1912 was approximately 30 per cent; in the Brigham series to 1929 it was 17 per cent, and during the last three years 11 per cent. Of the statistics in the last ten years, while the mortality in 1922-1923 was 16.9 per cent, during the last year of 1930-1931 it was 6.8 per cent. Nothing can tell the story better than this.

Cushing gives credit to the various factors that have made possible such marvelous advances, citing such technical improvements as Dandy's ventriculography and the introduction of electrical surgical devices; but what would all these things have mattered had there not been a Cushing? After all there is always some person with the genius and capacity for work which make great advances possible, and no one has done more for neurosurgery in the last thirty years than Harvey Cushing.

The Development of the Highest Motor Function in the Child. By M. S. Lebedinsky. With an Introduction by Prof. M. O. Gurevich and Prof. A. R. Luria. Pp. 159. Moscow: State Publishing Company, 1931.

In this remarkable monograph the author describes the results of an investigation of the highest nervous activity of children, especially the motor system, by using the experimental methods of Luria (*Arch. f. Psychiat.* **87**:471, 1929). The method is simple and consists of tapping a key the vibration of which is transmitted to a tambour and from there recorded on a drum. The simplicity of the method makes it possible to use it for experimental work with children. The author's research brings out significant data concerning the processes of excitation and inhibition as well as voluntary action in the growing child. As a control, the responses of mentally deficient children, as well as of normal adults, are used. The development of the regulating and the coordinating functions of the cortex, the influences of social environment, the acquisition of speech and the educational level all give definite and specific responses in the experiments. The data also bring out the fundamental differences between children, differences that are apparently basic or constitutional. The influence of emotion in upsetting the psychomotor behavior of the child is demonstrated with unusual but characteristic tracings; thus, when threats were used the motor response became completely disorganized, which was brought out clearly in the experimental curves. Whether fear as a primary emotion or the overstimulation of the frightened child under the influence of fear is responsible for the behavior cannot be stated definitely. The volume is full of sound, interesting observations.

In an extensive preface, Prof. A. R. Luria, whose method the author used, points out that intelligence tests deal with purely accidental data and do not give reliable information about the total development of a child. Instead of the very unrepresentative mental age he proposes the so-called neurodynamic age, which would give a better idea of the total development of the child, his motor system, his inhibitory processes, his social adaptations, etc. He points out that the author has gone far toward establishing a more objective method of studying and understanding the child.

It is a pleasure to see a monograph in educational psychology free from meaningless statistical tables, which brings out the fact that sound work done well with a few subjects is much more important than the tabulation of tests on 10,000 school children in some locality, even when it includes the standard deviation of the standard deviation.

Obituary

MICHAEL OSNATO

1886-1932

Sudden and unexpected death took Dr. Michael Osnato from active neurologic practice and productive participation in American neurologic activities on June 15, 1932. He had left New York hardly a week before for a short vacation in Germany and died suddenly on the train between Bremen and Berlin.

Michael Osnato was born on Nov. 22, 1886, in San Paolo Albanese, Italy, and came to this country with his parents while still a small child. He received his education in the New York public schools, and after being graduated from the DeWitt Clinton High School he entered the College of Physicians and Surgeons, Columbia University in the fall of 1902. He was graduated in 1906 with the degree of M.D.; he served internships in the Bellevue and Italian hospitals and then went into general practice.

In 1914, he first came in contact with neurology and psychiatry when he was appointed medical examiner in the bureau of deportation of the State Hospital Commission. In 1916, when he relinquished this position, Dr. Osnato decided to devote himself to neurology and secured a position in the Vanderbilt Clinic, department of neurology. Here he made the most of the opportunities offered him to learn neurology both in the clinic and in the laboratories of the College of Physicians and Surgeons. His progress was rapid as his determination to learn was genuine.

When our country entered the war Dr. Osnato at first remained at the College of Physicians and Surgeons, helping out with the neurologic teaching until he entered the army in the early part of 1918. In July of that year he was sent abroad with the rank of Captain as neuropsychiatrist to Base Hospital no. 102. At first he saw service with that hospital in Vicenza, Italy, and later was detached to become consultant in neuropsychiatry to the A. E. F. in Italy. He saw considerable service both at the front and in base hospitals until the end of the war. For his military service he was awarded by the Italian Government, the Croce di Guerra and the Order of the Italian Crown.

In February, 1919, Dr. Osnato was discharged from the army and returned to his neurologic practice and to his work in the Vanderbilt Clinic and the College of Physicians and Surgeons. In 1920, he first allied himself with the New York Post-Graduate Hospital, and, in 1926, when the service there was reorganized, he was appointed professor of

neurology and director of the neurologic department, which position he held at his death. His interest in his Alma Mater he maintained to the end, and from 1930 on he held the position of clinical professor of neurology in the College of Physicians and Surgeons.

Dr. Osnato was always active in the neurologic and psychiatric societies. He was a member of the local and national societies and the New York Academy of Medicine. In 1930-1931, he was chairman of the Section on Neurology and Psychiatry in the Academy. He was elected to membership in the American Neurological Association in 1920.

Michael Osnato left behind many friends to miss him. He made friends readily, and those he made he kept. His was a life of struggle. It was the story of an immigrant boy who worked his way up to recognition by his innate personality characteristics and his ability for hard work. The position he attained was all the more deserved because it was self-earned. His friends regret the most in his passing the fact that he died while still young, before he had reached what they all hoped would be his most productive years in the maturity of his career.

LOUIS CASAMAJOR, M.D.

News and Comment

TENTH INTERNATIONAL CONGRESS OF PSYCHOLOGY

The tenth international congress of psychology will be held in Copenhagen, Aug. 22 to 27, 1932, at the University Festival Hall, under the Protection of H. M., the King of Denmark. A provisional program includes papers to be presented by one hundred and thirty authors from about twenty different countries. A series of social meetings and excursions to points of interest has been arranged for members of the congress and ladies accompanying them. The secretary for the National Committee is Edgar Rubin, Studiestraede 6, Copenhagen K, Denmark.

THE CHICAGO SOCIETY FOR PERSONALITY STUDY

There has recently been organized the Chicago Society for Personality Study, consisting of psychiatrists, psychologists, sociologists, educators, physiologists and others, with the object of integrating the sciences in a scientific body devoted to the study of personality in all its phases, normal or abnormal, child and adult. Its membership is limited to one hundred. It contains the best students of personality problems and human behavior connected with various scientific and educational institutions in and around Chicago.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Secretary*

The four hundred and first meeting of the society was held in conjunction with the Harvey Cushing Society at the Peter Bent Brigham Hospital on May 6, 1932. Dr. W. Jason Mixter presided. The minutes of the previous meeting were omitted. Dr. Cushing presented a clinic of cases of tumor of the brain. About one hundred and fifty members and guests were present.

THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system, and to disseminate knowledge in this department of medicine.

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CONTENTS