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THE SURGICAL MORTALITY PERCENTAGES PERTAINING TO A SERIES OF TWO THOUSAND VERIFIED INTRACRANIAL TUMORS

STANDARDS OF COMPUTATION

HARVEY CUSHING, M.D.
BOSTON

In calculating these mortality percentages the standard which we have set for ourselves is that *every death in hospital following an operation from any cause whatsoever, no matter how long the interval, is recorded as a postoperative fatality.* There is no possibility of any exception being made to this rule, however justifiable it might appear to be, for the record is automatically made by a secretary from the completed case record after the patient's hospital discharge, living or dead. Were this precaution not taken, those personally interested would, now and then, find the temptation to evade an admittedly severe standard well nigh irresistible.

But should one begin to make exceptions to the rule, there would be no end to them—a patient about to be discharged after a successful operation has a perforated gastric ulcer; another gets out of bed at night to go to the toilet, trips over an obstruction and dies in a few hours from a fracture of the base of the skull; another during an epidemic of influenzal pneumonia has a fatal infection; still another has a coronary thrombosis five weeks after making a perfect recovery from a tumor extirpation. Similar examples might be multiplied, and were they not automatically recorded as postoperative deaths, the temptation to exclude fatalities from other complications more obviously postoperative, such as pulmonary embolism, postoperative pneumonia, tuberculous meningitis after the successful removal of a tuberculoma, and so on, would be difficult to resist, since no sharp line can be drawn between those due and those not due to the operation.

As there is no convalescent home to which patients may be transferred, and since a large proportion of them come from a distance, they are necessarily retained in hospital longer than would otherwise be necessary,[1] and there is ample time for intercurrent disorders to develop

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This paper represents the last portion of a communication made at the International Neurological Congress in Bern, September, 1931. The mortality statistics for tumors of different kinds and situations, separately considered, which form the basis of these tables, will be published elsewhere in monograph form.

1. The average sojourn in the hospital in the last 100 consecutive cases of surgically verified tumors has been thirty-nine days.

which bring additional risks. Another element that tends to increase the percentage of postoperative fatalities among histologically verified tumors is the high incidence (averaging over 90 per cent) of postmortem examinations that are secured. Owing to this, many tumors are identified at autopsy that otherwise, owing to negative explorations, would have remained in the list of tumors unverified. What is more, we frequently retain in hospital for indefinite periods—five months in one instance—patients whose tumors we have failed surgically to verify, with the understanding that in the end permission for an autopsy will be given.

Then, too, as was stated in another connection, in the process of working out the life history of these growths the case mortality in all types of malignant glioma should theoretically be 100 per cent; for if operations for recurrences are systematically pursued to the end, it is almost a certainty that the last of them will be followed by a postoperative fatality. With all these things to consider, it is obvious that the operative statistics of two surgeons with equal skill and experience may legitimately vary within wide limits.

In all calculations of operative-mortality percentages there is still another element to consider: viz., *What is and what is not to be recorded as "an operation"?* Even though they may be attended with risk and lead to a fatality which permits postmortem verification of a tumor, we exclude, as all others would do, the simple punctures—lumbar, cisternal, transsphenoidal or ventricular. Nor do we record as operations the minor surgical procedures necessary for the securing of muscle from the patient's leg, nor those for blood transfusions nor for ventriculography, even though the last procedure may at times be hazardous and occasionally lead to a fatal issue. We do, however, record as separate operations those requiring more than one session for their completion, as they are almost invariably critical performances; and for the same reason we also record emergency reelevations of osteoplastic flaps necessitated by postoperative clot formation.

Then there is a final point to be decided: viz., *When does the operation begin?* Does it begin with the ward preparations, with the anesthetic, or only after an incision has been made? In many patients with brain tumors having an advanced syndrome the condition at best is serious. Sudden respiratory failure may occur should a patient with a cerebellar tumor strain to expel a preparatory enema, or have the neck unduly twisted while the scalp is being shaved, or, in days when ether anesthesia was employed, from the early effects of the anesthetic. Many patients after such accidents have been operated on immediately under artificial respiration, and a few of them have thus been saved.

No surgeon would conceivably hesitate for a second to face emergencies of this kind, though they are very bad for one's mortality per-

centages. In the last fifty consecutive operations for acoustic tumor, for example, one of the two recorded fatalities (table 1) was that of a patient operated on in an agonal state after a sudden respiratory failure. Had the surgeon been thinking of his score rather than of possibly saving a life, his mortality figures for this particular group of cases would have been cut in half. One must draw the line somewhere, and it seems fair to do so with the incision of the scalp.

(1) *Mortality Percentages for the Series as a Whole.*—My experience in neurosurgery may be divided into three decades: the first, from 1901 to 1912, when a beginner at the Johns Hopkins Hospital; the second, from 1912 to 1922, with its lost ground difficult to regain, due to a two years' absence in France; and the third, from 1922 to 1931,

TABLE 1.—*Case-Mortality Percentages for Acoustic Tumors in Successive Groups of Fifty*

Dates	Time Interval	Number of Cases	Number of Operations	Number of Deaths	Case Mortality, per Cent	Operative Mortality, per Cent
Jan. 18, 1906 to Oct. 5, 1915	9 yrs. 9 mos.	21	32	6	28.6	18.7
Jan. 22, 1916 to Feb. 13, 1923	7 yrs. 1 mo.	50	64	10	20.0	15.6
March 6, 1923 to Sept. 6, 1927	4 yrs. 6 mos.	50	62	7	14.0	11.3
Oct. 18, 1927 to July 1, 1931	3 yrs. 9 mos.	50	58	2	4.0	3.4

TABLE 2.—*Comparison of Operative Mortality Percentages for Verified Tumors of Four Major Groups Divided into Three Periods*

	Hopkins Series to 1912, per Cent	Brigham Series to 1929, per Cent	July, 1928, to July, 1931, per Cent
Gliomas (varia)	30.9	17.8	11.0
Pituitary adenomas	13.5	5.3	5.7
Meningiomas	21.0	10.3	7.7
Acoustic tumors	25.0	11.5	4.4

during which period detailed week-to-week statistical records with annual compilations of the intracranial tumors have been kept by Dr. Eisenhardt, who made a detailed report on the subject two years ago.[2] A highly condensed table (table 2), limited to the operative mortality percentages of the four major groups of verified tumors, as given in her paper, contrasted with the results in the past three years, is appended.

(2) *Mortality Percentages Year by Year.*—Table 2 shows, as would be expected, a progressive improvement in the figures that has come with the experience of later years. As a matter of fact, during each year of the last decade there has been a definite tendency to an annual lowering of the case and operative mortality, as shown in table 3. This table gives the mortality figures for the cases in which the patients were

2. Eisenhardt, L.: The Operative Mortality in a Series of Intracranial Tumors, Arch. Surg. **18**:1927 (April) 1929.

discharged, living or dead, between May 1 and May 1 of each successive year. And were the figure included for the 549 patients admitted or readmitted with tumors unverified during these years, the percentages would be still lower in view of the relatively few fatalities (2.9 per cent case mortality and 2.5 per cent operative mortality) in the unverified group.[3]

Table 3 points out what the operating members of the neurosurgical staff were themselves conscious of; namely, that in 1927 and 1928, on the introduction of electrosurgical methods, a number of patients, whose tumors when exposed had been regarded as inoperable, were called back and reoperated on, with a high mortality rate, partly because of the dangerous procedures undertaken and partly because of inexperience with electrosurgical principles.

TABLE 3.—*Annual Statistics of Operations for Verified Tumors Including New and Old Cases from 1922-1931*

Successive May 1 to May 1	Number of Patients	Patients Operated On	Number of Operations	Post-operative Deaths	Case Mortality, per Cent	Operative Mortality, per Cent
1922–1923	104	94	130	22	23.4	16.9
1923–1924	156	140	190	26	18.6	13.7
1924–1925	137	113	142	21	18.5	14.7
1925–1926	155	133	172	25	18.8	14.5
1926–1927	184	161	217	24	14.9	11.0
1927–1928	185	149	183	28	18.7	15.3
1928–1929	205	179	226	26	14.5	11.5
1929–1930	178	147	191	24	16.3	12.5
1930–1931	200	170	219	15	8.8	6.8
Total	1,504	1,286	1,670	211	16.4	12.6

Apart from the figures for this particular 1927-1928 twelve-month, there has been a slowly progressive decline in the mortality percentages, with a pronounced drop during the last year, which came somewhat as a surprise, even though we were aware that it has been a good year. This is all the more gratifying in view of the fact that as time goes on the clinic carries an ever increasing burden of patients readmitted for recurrence of symptoms; and though reoperations for medulloblastomas and glioblastomas are perhaps less readily undertaken than formerly, even the most conservative among us can hardly refuse to reoperate on the less malignant lesions like meningiomas, neurinomas and astrocytomas when symptoms recur.

(3) *Mortality Percentages for the Separate Tumor Groups.*—These calculations are particularly illuminating in that they show how the percentages tumble as soon as the life history of any particular tumor has been thoroughly worked out. Of only a few tumors can it be said that this

3. It should be clearly understood that the computations on which the figures in table 3 are based represent each year's work taken by itself, including, therefore, both new and old patients, with primary operations as well as those for recurrences.

has been done with sufficient thoroughness to affect the operative results, but these few furnish striking illustrations. For example: The operative mortality of the once dreaded acoustic tumors (as shown in table 1) has fallen for each successive fifty cases from a 28 per cent to 20 per cent to a 14 per cent to 4 per cent case mortality. The present operative mortality for the chromophobe adenomas, formerly about 13 per cent, has also dropped to slightly below 4 per cent. The figures for the cerebellar astrocytomas, practically unknown ten years ago, have fallen from a 28 per cent case mortality for the first twenty-five patients to 4 per cent for the last twenty-five cases. Even the highly malignant glioblastomas of the cerebrum have shown a drop from 24 per cent for the whole series to 14 per cent; and now that the cerebellar medulloblastomas are better understood, even these—the most disheartening of all brain tumors—may be expected to show a great improvement in their operative percentages.

In table 4, the mortality figures have been assembled, not only for the eleven major subdivisions of the *verified tumors*, but separately for the *unverified tumors*. The table has been divided into two sections, the first giving the operative figures for the entire series, which carries the heavy load of fatalities of the early years of inexperience. In the second section the figures are only those for the new cases that first came under observation in the three-year period from July 1, 1928, to July 1, 1931.

This table, therefore, by the exclusion of old cases, readmitted during the last three-year period because of the symptomatic recurrence of tumors imperfectly treated at an earlier day, gives a clearer idea of what results may reasonably be expected of those newcomers to neurosurgery who can profit, not only by the present-day improvements in technic, but by the existing state of knowledge regarding the life history of the various lesions. And should they take warning from the experience of others and avoid over-radical attempts to remove large congenital craniopharyngiomas, refrain from operating on obviously metastatic tumors, and refuse all secondary operations for recurrences, they could easily attain a case mortality of 4 or 5 per cent for the whole.

Factors Influencing Mortality Percentages.—The wholesale statistics given in the last three tables will serve, I hope, to give others who engage in like tasks something to play against. The more important figures are those which pertain to special tumors in special situations, and they will be found published in a monograph in which the various lesions are separately considered. Had it not been for the industry of Dr. Eisenhardt, these calculations would never have been made; but now that they have been, they may well enough be published even though there is no reason for taking pride in what they show. The high mortality percentages of the early cases still cast their shadow over the figures for the complete series.

TABLE 4.—*A Comparison of Operative Mortality Figures for the Entire Series with Those of the Past Three Years*

Intracranial Tumors Verified	Entire Series (1902-1931)						New Cases July 1, 1928–July 1, 1931				
	Number of Patients	Patients Operated On	Number of Operations	Post-operative Deaths	Case Mortality, per Cent	Operative Mortality, per Cent	Number of Patients	Number of Operations	Post-operative Deaths	Case Mortality, per Cent	Operative Mortality, per Cent
I. Gliomas	**862**	**780**	**1,173**	**202**	**25.9**	**17.2**	**198**	**282**	**31**	**15.7**	**11.0**
Cysts undifferentiated	63	63	89	6	9.5	6.7	3	4	0	0.0	0.0
Differentiation impossible	74	61	88	12	19.7	13.6	4	4	2	50.0	50.0
Atypical and transitional	38	34	60	15	39.5	25.0	4	7	1	25.0	14.3
Astrocytomas											
Cerebral	164	149	221	23	15.4	10.4	41	52	2	4.9	3.8
Cerebellar	91	90	134	15	16.6	11.2	29	34	1	3.4	2.9
Glioblastoma multiforme	208	183	272	66	36.1	24.2	73	120	17	23.3	14.1
Medulloblastomas											
Cerebral	18	16	26	3	18.8	11.5	3	3	0	0.0	0.0
Cerebellar	68	64	99	25	39.0	25.2	15	19	5	33.3	26.3
Astroblastomas	35	31	58	10	32.2	17.2	7	10	1	14.3	10.0
Spongioblastoma polare	32	31	36	8	25.8	22.2	7	12	1	14.3	8.3
Oligodendrogliomas	27	26	46	4	15.4	8.7	8	13	0	0.0	0.0
Ependymomas											
Cerebral	6	6	11	2	33.3	18.2	0	0	0	....	....
Cerebellar	19	16	19	5	31.3	26.3	4	4	1	25.0	25.0
Pinealomas	14	6	8	6	100.0	75.0	0	0	0	....	....
Ganglioneuromas	3	3	4	2	66.6	50.0	0	0	0	....	....
Neuro-epitheliomas	2	1	2	0	0.0	0.0	0	0	0	....	....
II. Pituitary adenomas	**360**	**349**	**403**	**25**	**7.1**	**6.2**	**59**	**70**	**4**	**6.8**	**5.7**
Chromophobe and mixed	287	278	322	17	6.1	5.2	54	65	3	5.5	4.6
Chromophile	73	71	81	8	11.2	9.8	5	5	1	20.0	20.0
III. Meningiomas	**271**	**260**	**489**	**54**	**20.8**	**11.0**	**69**	**103**	**8**	**11.6**	**7.7**
IV. Acoustic tumors	**176**	**171**	**219**	**25**	**14.6**	**11.4**	**41**	**45**	**2**	**4.9**	**4.4**
V. Congenital tumors	**113**	**106**	**160**	**23**	**21.7**	**14.4**	**17**	**25**	**4**	**23.5**	**16.0**
Craniopharyngiomas	92	87	130	19	21.8	14.6	14	19	3	21.4	15.8
Cholesteatomas	13	13	18	3	23.1	16.6	3	6	1	33.3	16.6
Teratomas	4	2	5	0	0.0	0.0	0	0	0	....	....
Dermoid cysts	2	2	4	0	0.0	0.0	0	0	0	....	....
Chordomas	2	2	3	1	50.0	33.3	0	0	0	....	....
VI. Metastatic and invasive	**85**	**63**	**80**	**18**	**28.6**	**22.5**	**10**	**11**	**4**	**40.0**	**36.4**
VII. Granulomatous tumors	**45**	**40**	**49**	**15**	**37.5**	**30.6**	**4**	**5**	**0**	**0.0**	**0.0**
Tuberculomas	33	30	35	15	50.0	42.9	4	5	0	0.0	0.0
Syphilomas	12	10	14	0	0.0	0.0	0	0	0	....	....
VIII. Blood vessel tumors	**41**	**37**	**59**	**6**	**16.2**	**10.2**	**7**	**10**	**1**	**14.3**	**10.0**
Hemangioblastomas	25	24	44	6	25.0	13.6	7	10	1	14.3	10.0
Malformations	16	13	15	0	0.0	0.0	0	0	0	....	....
IX. Sarcomas (primary)	**14**	**12**	**17**	**6**	**50.0**	**35.3**	**0**	**0**	**0**	....	....
X. Papillomas	**12**	**11**	**23**	**3**	**27.3**	**13.4**	**1**	**2**	**0**	**0.0**	**0.0**
XI. Miscellaneous	**44**	**41**	**63**	**5**	**12.2**	**7.9**	**6**	**9**	**1**	**16.6**	**11.1**
Totals	**2,023**	**1,870**	**2,735**	**382**	**20.4**	**13.9**	**412**	**562**	**55**	**13.3**	**9.8**
Unverified	**859**	**496**	**557**	**12**	**2.4**	**2.2**	**66**	**73**	**0**	**0.0**	**0.0**
Combined totals	**2,882**	**2,366**	**3,292**	**394**	**16.6**	**11.9**	**478**	**635**	**55**	**11.5**	**8.7**

It has been erroneously assumed in some quarters that the improved results of recent years are due to earlier diagnoses rather than to greater skill and experience—in other words, that the neurosurgeon of today deals with a selective list of relatively favorable lesions. This assumption is far from the actual facts. In reality, each year the problems become more difficult than those of the year before. The proportion of patients admitted as "forlorn hopes" in the terminal stages of their malady, often after ill-judged procedures at the hands of surgeons with little or no neurosurgical training, is as large as it ever was. What is more, each succeeding year sees tumors surgically exposed, like tumors of the third ventricle, which formerly were regarded as hopelessly inaccessible. Hence, all things considered and in spite of the constant improvement in diagnosis and surgical technic, the operations as time passes become increasingly critical and difficult.

The principal steps that have made it possible not only to attack the more formidable problems of the present day but at the same time to lower the operative mortality may be chronologically enumerated: (1) the generally accepted methods of decompression to relieve tension; (2) such irreproachable wound healing that secondary infections are practically unknown; (3) the separate closure of the galea by buried fine black silk sutures, which has made the once dreaded fungus cerebri nigh forgotten; (4) in place of ether inhalation, the introduction by de Martel of local anesthesia, now supplemented when necessary by the rectal administration of tribromethanol; (5) the more precise tumor localization which in obscure cases Dandy's ventriculography permits us to make; (6) the use of a motor-driven suction apparatus as an indispensable adjunct to every operation, and (7) the successive improvements in methods of hemostasis, which, since 1927, have been most advantageously supplemented by the introduction of electrosurgical devices.

But the operation itself is by no means the whole story. The aftercare is equally important, for unsuspected complications may arise at any moment, which if overlooked or neglected may wholly turn the scale. This has been well summarized in Dr. Eisenhardt's paper of two years ago.

> Rarely is more than one major operation for tumor scheduled for one day. Most of the operations are carried through under local anesthesia, and all are started in this way. Patients who have been subjected to a craniotomy are not moved from the operating suite until the danger of the formation of a postoperative extradural clot has passed. After critical cerebellar operations, particularly if inhalation narcosis has been necessitated, the patients are usually left on the table for several hours until they have fully recovered, and they are often kept in the operating suite for a number of days. Those with deglutitory difficulties must often be fed through the nares for prolonged periods. For charity patients who are in a critical condition, from this or some other cause, special nurses are provided and paid for out of a fund donated for the purpose.

Since this was written an additional safeguard has been made; namely, in providing for the undivided service of a highly trained nurse, who, while the surgeons are engaged in their time-consuming operations, can devote her attention to the more critically ill of the thirty or forty patients, either awaiting operation or already operated on, whom we sometimes have under observation at one time. Unquestionably, many lives have been saved in this way, for less experienced nurses or junior house officers can hardly be expected to appreciate the significance of symptoms which indicate that something is going wrong with a patient recently operated on for a brain tumor; a few hours' delay due to the misinterpretation or neglect of a warning signal may mean the difference between a fatality and a recovery.

HISTOLOGIC CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

G. ROUSSY, M.D.
AND
C. OBERLING, M.D.
PARIS, FRANCE

An interest in tumors of the central nervous system, due to the development of neurosurgery and the advent of roentgenotherapy, has caused us to combine lines of research that up to the present have been followed in one or the other realm separately. This new attack, carried on over a period of more than two years, is based on material consisting of 251 tumors. We have made certain modifications in the details of the classification proposed by one of us (G. R.) with Lhermitte and Cornil in 1924. This has been carried out with the help of our personal documents gathered since that time, and with the help of the new technic and studies that have appeared recently, particularly those of Harvey Cushing, Percival Bailey and Wilder Penfield.

The classification that we propose comprises essentially the same general ideas as that formerly reported. We seek, on the one hand, to simplify the nomenclature in order to render it more comprehensible to neurologists and at the same time to take into consideration, as much as possible, the clinical and anatomic factors. On the other hand, we shall endeavor to remain strictly in the realm of morphology, and to avoid making absolute deductions from the histologic appearances as to the origin of neural tumors.

In this work we shall try to retain some of the essential facts that are demonstrated by our researches. We shall refer for greater detail to the publication that has just appeared in the series entitled the "Atlas of the French Association for the Study of Cancer." [1]

In company with most of the authors we recognize five large groups of tumors. We shall designate as gliomas the tumors formed by the interstitial neuroglia, as ependymochoroid tumors the neoplasms constituted by the ependyma or by the covering of the choroid plexus, and as ganglioneuromas the tumors due to a proliferation of ganglionic cells and neurons.

Besides these three groups of tumors, in which one finds essentially the cellular varieties of adult nerve tissue in their diverse evolutionary

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1. Roussy, G., and Oberling, C.: Atlas du cancer, Paris, Félix Alcan, 1932, nos. 9 and 10.

and involutionary forms, there also exist tumors in which the cells resemble more or less closely the elements of the embryonic nerve tissue, not only in their morphologic but also in their evolutionary characteristics.

Certain of these tumors, formed essentially of neuroblasts and spongioblasts, recall the appearance of the neurospongium; these are neurospongiomas. Others reproduce the structure of nerve tissue in a still earlier stage of development, in the stage of the neuro-epithelium; these are neuro-epitheliomas.

GLIOMAS

Gliomas are divided into three varieties according to the nature of the cells that predominate. These are: the astrocytomas, formed essentially by astrocyte elements, the oligodendrocytomas, due to a profuse multiplication of the oliogodendroglia elements, and the glioblastomas, which are formed by young cells of indifferent character, resembling more or less the glioblasts of the embryonic nervous system.[2]

Astrocytomas.—We shall not stop to consider astrocytomas at length, as their structure is well known. We believe the somewhat schematic separation into fibrillar and protoplasmic astrocytomas should be abandoned. In general, it is difficult to distinguish between the two types, since very different aspects may be encountered in the same tumor. It is possible to distinguish from their general appearance the following groups: very fibrillar astrocytomas, grossly fascicular subependymal astrocytomas, sparsely fibrillar or afibrillar astrocytomas, gigantocellular astrocytomas and pseudopapillary astrocytomas.

It seems interesting to stress the importance of the regressive phenomena and the frequent secondary alteration processes, which can modify considerably the morphologic texture of tumors.

Thus one often sees in the astrocytomas cells of simplified structure, in which the voluminous cytoplasmic bodies are deprived of dendrites and possess only one perivascular foot, which is sometimes very indistinct. These elements resemble astroblasts, such as one sees in embryonic nerve tissue; more often, however, they are not embryonic elements, but degenerated astrocytes. We have observed, in fact, similar cells in the encephalitic lesions caused by radium.

Another form of degeneration is characterized by the appearance of voluminous cells which O. Lotmar has compared to ameboid cells; however, these voluminous cells are distinguished from the ameboid

2. To simplify and unify the terminology of neurologic elements and gliomas, we have designated the different neuroglia cells by the terms, astrocytes, oligodendrocytes and microgliocytes; the tumors formed from one or the other of these elements are called astrocytomas, oligodendrocytomas and microgliocytomas (the existence of the latter variety of neoplasm is debatable).

cells by the length of their expansions. They resemble closely the fat-filled glia cells of Nissl, that is, the hypertrophic, sometimes monstrous astrocyte elements that are found in the vicinity of areas of degeneration. It is interesting to note that the gigantocellular aspects are found in those slowly proliferating astrocytomas in which the phenomena of disintegration are particularly marked.

In certain astrocytomas there is some tendency toward peritheliomatous structure.

Oligodendrocytomas.—These correspond, for the most part, to the description that Bailey has given. To the naked eye they seem limited and form a rosy grayish mass of variable consistency, sometimes firm, sometimes friable. They are almost constantly the seat of calcareous incrustations which make them easily visible on roentgen examination.

The histologic picture of oligodendrocytomas is characteristic and, as Bailey said, easily recognized even with ordinary methods. In the typical cases, the tumor tissue presents—besides the calcareous incrustations—an absolutely uniform aspect. It consists of small cells of which the round nuclei, richly sprinkled with dustlike chromatin, seem to be of the same size. Nuclear monstrosities and mitoses are rare.

The cytoplasm of the tumor cells is barely visible and appears sometimes as a finely granular mass and sometimes as a clear space around the nucleus. The latter aspect is seen especially in sections fixed in a solution of formaldehyde containing potassium bromide and stained by the usual methods. The tumor cells then present a peculiar vesicular aspect. Among the cells, one sees a fibrillar substance, which ensheathes single cells or groups of cells and serves as a small incasement.

Certain oligodendrocytomas are characterized by the presence of a mucicarminophile substance which occupies the intercellular spaces and is found in the form of fine droplets in the very interior of the tumor cells.

A mucous glioma is found attached thus to groups of oligodendrocytomas. It is interesting to note that the formation of mucus, which represents one of the peculiar characteristics of the oligodendrocyte (mucocytic degeneration of Grynfeltt, Pelissier and Pages), is also found in the tumors formed by these cells.

As shown by impregnation methods, the great majority of neoplastic cells demonstrate characteristics of oligodendrocytes; that is, they have small cytoplasmic bodies from which emanate smooth and somewhat ramified expansions. But these tumors also contain astrocytes which are grouped around the blood vessels and constitute, in certain cases, a true angio-astrocyte stroma in the mesh of which the oligodendrocytes are found. These tumors are always rich in cellular forms of an ambiguous character, resembling both the astrocyte and the oligodendrocyte; to all appearances these are transitional forms.

Besides these tumors, in which the oligodendrocyte character is demonstrated, there exist others that probably belong to the same category although their morphologic characters are somewhat different.

These are the gliomas composed of cells with elongated nuclei comparable to rod cells. The cytoplasmic body is very thin, and the impregnations show one or two rigid and smooth prolongations which emerge as two cellular poles. These elements are grouped in bundles, and assume aspects that resemble closely certain peripheral gliomas or neurinomas. Certain authors (e. g., Josephy) have described them under the name of central neurinoma.

Bailey has interpreted them as spongioblastomas, thinking that the tumor cells correspond to very young glia cells, that is, unipolar or bipolar spongioblasts. It seems logical to consider these elements as oligodendrocytes and thus draw a parallel between the fascicular oligodendrocytomas and the neuromas, the ones in a central position and the others in a peripheral position. Their structural resemblance points to a parent relationship between the oligodendrocyte and the Schwann cell.

Glioblastomas.—These correspond to the polymorphic gliomas of Roussy, Lhermitte and Cornil and to the spongioblastomas of Bailey and Cushing. Glioblastomas are essentially made up of young neuroglia cells, probably of an astrocytic nature, because all transitions between astrocytomas and glioblastomas are present. However, even in the characteristic glioblastomas, one always finds typical adult astrocytes.

In regard to the pseudorosettes of degeneration that one frequently finds in these tumors, the term "rosette" as commonly used often designates very different formations. To avoid confusion, we shall apply the term rosette, or true rosette, to spherical formations the center of which consists of a dense mass of fibrils from which cells emanate radially. These true rosettes are found most usually in neuroblastic tumors, in neurospongiomas and in embryonic sympathomas.

These true rosettes may be contrasted with pseudorosettes in which the center is not distinctly fibrillar. Some of these rosettes result from a perivascular expansion of fibrillar cells, for example, the perivascular pseudorosettes; others are due to a radial grouping of cells around a focus of necrosis; such are the pseudorosettes of degeneration, particularly frequent in glioblastomas.

Many other authors employ the term rosettes to designate the radial grouping of epithelial cells covering a tubulous cavity. These formations, which are met with in neuro-epithelial or ependymal tumors, may be conveniently designated by the terms tube or canal, since they resemble a tube or a primitive neuro-epithelial canal, which, however, cannot qualify as a rosette.

In other respects, the study of glioblastomas does not furnish new information except to confirm the characteristic of particularly pronounced malignity contrasted with the relative benignity of other gliomas.

EPENDYMOCHOROID TUMORS

In most cases, one finds that a distinction between ependymal tumors and choroid tumors is impossible.

A. Ependymal tumors are designated under the generic name of ependymoma. They furnish three different aspects: the ependymocytoma (the ependymoma of Bailey), made up of cubical cells without fibrillar prolongations; the ependymoblastoma, made up of ependymal cells with fibrillar prolongations, and the ependymoglioma, in which there is a proliferation consisting of ependymal and astrocyte elements.

The latter tumors are generally very small neoplasms which are seen in the region of the fourth ventricle, in the aqueduct and especially in the central parts of the medulla oblongata and the spinal cord, where the cavernous transformation gives rise to syringomyelic cavities.

In typical cases the ependymal cells contain multiple vesicles, true ependymal cavities, around which the astrocyte elements constitute a glial matting, more or less dense and very cellular. The quantitative proportion of these two constituent elements is various; sometimes the ependymal elements and sometimes the astrocyte elements predominate. One finds, thus, all the intermediary variations among the ependymogliomas, and because of the preponderance of the ependymal elements these approach the ependymomas and the ependymogliomas. They can be distinguished from gliomas only by the presence of several ependymal cavities.

The interpretation of these tumors has aroused numerous discussions on the part of authors who have studied the question (Ribbert, Bonome, Vonwiller, Bielschowsky and Unger, Tannenberg, Orlandi, Antoni).

Without wishing to go into detail on a subject that brings forward, among others, the whole problem of syringomyelia we point out that probably the histogenetic mechanism of these combined ependymoglial proliferations is not always identical. One can believe, in fact, that in certain cases there may be an ependymal tumor in which some elements undergo an astrocyte transformation. That is the idea which occurs to one when the ependymal element is distinctly predominant, and one observes numerous transitional forms among the ependymal cells and the astrocyte elements.

One can also believe that in other instances there may be an ependymal and a glial proliferation at the same time.

In a final series of cases it might be admitted that we are dealing in the last analysis with a glioma that involves a proliferation or includes

the ependymal formations that are found in its vicinity. It must be remembered in this regard that ependymal aberrant offshoots are frequent, not only in the immediate neighborhood of the normal ependymal cavities, but even at a distance. Their existence has been demonstrated in various regions of the hemisphere and even in the white subcortical substance (Arnold, Ribbert, Guillery, Babonneix and Lhermitte). It is to be understood, therefore, that ependymal inclusions may be found even in gliomas situated at a distance from the ventricular cavities.

Theoretically, one can distinguish true ependymogliomas (tumors belonging to the first two categories) from gliomas with ependymal inclusions (second category), but in practice that distinction is not always possible.

B. Choroid tumors are most often papillomas. Epitheliomas are rare.

The choroid papillomas show a well developed stroma formed by vessels enclosed by connective tissue, often edematous and myxoid, containing calcospherites or undergoing pseudocystic transformation. One sometimes finds xanthomatous cells, true lipophages comparable to those that infiltrate the papillary axes of certain papillomas of the kidney.

The epitheliomas of the plexus often assume a papillary character. Certain epitheliomas of the choroid plexus are characterized by the presence of malpighian elements to which Boudet and Clunet first called attention.

These authors studied a papillary tumor that developed at the base of the brain and adhered to the cerebrum at the level of the fissure of Bichat. Histologic examination showed numerous axes of vascular and connective tissue covered by a malpighian epithelium of incomplete corneal development, with multiple and varied secondary modifications. Boudet and Clunet said that analogous malpighian tumors have been observed on different occasions in the fourth, and notably in the third ventricle. Following that work, similar observations were published by Letterer, I. Bertrand and by us.

To interpret the peculiar structure of these tumors, Boudet and Clunet have considered the possibility of a malpighian metaplasia of the choroid epithelium. They failed to note, however, that malpighian metaplasia of the choroid epithelium is rare, if it exists at all, and that the malpighian tumors develop in the vicinity of the base of the cranium (third ventricle). It might be more logical to think of an embryonic malformation since the malpighian heterotopia coming from the anterior endoderm is frequent in that region.

GANGLIONEUROMAS

The tumors formed by more or less typical ganglion cells and nerve fibers are rare. We found one single example among 250 cerebral

tumors examined. The study of that tumor did not furnish any new information worthy of mention.

NEUROSPONGIOMAS

Neurospongiomas (medulloblastomas of Bailey and Cushing) are among the most frequent tumors of the central nervous system, and our study places them in order of frequency immediately after the gliomas and the ependymal tumors. These tumors occur most often in the region of the cerebellum and are found there most often in young persons. Among the patients examined by us, three were less than 10 years old (6, 6½ and 8½), eight from 10 to 20 years old (10, 11, 12, 13, 18, 19 and 20) and three were over 20 years of age (22, 26 and 41). These facts agree with those published by other authors; in Cushing's study the proportion of patients of less than 10 years of age was higher.

The general character of these neoplasms, as well as their essential morphologic characteristics, has been sufficiently described in the work of Bailey and Cushing and in a monograph by Cushing. The utilization of various methods of silver impregnation demonstrated to us that the fibrillar substance contained in the neoplastic tissue is essentially formed by these neurofibrils. It also appears that the greater part of the tumoral cells correspond to apolar and unipolar neuroblasts. As for the cells with very voluminous nuclei, it is sufficient that they present multiple prolongations and a distinctly developed cystoplasmic body with a neurofibrillar network; these are multipolar neuroblasts. Besides these relatively typical cellular and easily identified forms, one finds numerous abnormal cells, with multiple nuclei and supernumerary and partially disintegrated prolongations; in these the polymorphism precludes all description.

Then again it is impossible to exclude the participation of the spongioblastic elements in the constitution of these tumors; we here have the impression that in certain of them the spongioblasts are numerous. One may thus distinguish essentially between neuroblastic neurospongiomas and neurospongioblastic neurospongiomas.

The nature of all the elements that enter into the constitution of these tumors is not definitely established, and that problem demands more research; besides, the nomenclature that is certain to designate these neoplasms is itself too cluttered.

We believe that it may be possible, from now on, to eliminate the terms gliosarcoma or glioblastic sarcoma (Schmincki); the word sarcoma evidently cannot be applied to neoplasms in which a nervous origin is demonstrated. Similarly, the term spongioblastoma (Globus and Strauss, Ribbert) is hardly more indicative unless one pays no attention

to the preponderance of neuroblastic elements. As for the term medulloblastoma, because of the authoritative character of the work of Bailey and Cushing, this term is used by many other workers, but we believe that it, too, is subject to criticism.

In fact, the idea that the medulloblast or the indifferent cell may be a bipotential element, glioblastic and neuroblastic at the same time, is argumentative. Besides, our own researches have led us to admit that it is not indifferent but neuroblastic cells that constitute the predominating element of these tumors.

The terms neurocytoma, neuroblastoma and neurogliocytoma (Marchand, Wright, Vanzetti, Masson and Dreyfus) seem to us too exclusive, since they have only in view distinctly definite cellular categories. In reality these tumors do not consist of pure cellular cultures, arrested at a certain point in their development; they are formed by elements that make up the neurospongium. For this reason we prefer the term neurospongioma.

NEURO-EPITHELIOMAS

The term neuro-epithelioma has quite often contributed to the confusion of the classification of tumors of the nervous system. In applying the term to all the neural tumors in which the cells take on the semblance of epithelial cells, one succeeds in bringing together the various tumors into one group: gliomas with ependymal inclusions, pseudopapillary astrocytomas, ependymochoroid tumors and the neurospongiomas themselves.

It is convenient to reserve the term neuro-epithelioma for tumors in which neuro-epithelial cells, that is, nerve cells in the first stage of development, predominate. Tumors formed exclusively of primitive neuro-epithelial cells hardly exist; if they do, their nervous nature cannot be recognized, since nothing can distinguish them from an ordinary cylindric epithelioma.

One always finds, in addition to primitive neuro-epithelial cells, various neuroblastic or spongioblastic elements, and quite often one finds even cells that have reached the end of their development and present the characteristics of ganglionic or adult neuroglial cells.

Such tumors are found only exceptionally in the central nervous system. They are more frequently observed in the retina, in the sacrococcygeal region, where they develop from medullary vestiges, and also in teratomas.

Microscopically, their structure is very polymorphic. In certain sections the aspect is that of an epithelioma made up of cavities and papillary formations covered by cylindric or cylindrocubical epithelium arranged in a single layer.

Moreover, the epithelial lining has a tendency to be stratified; the epithelial cells, considerably elongated, take the semblance of spongioblasts. Their apical surface bears a cuticle frequently provided with cilia; their basal extremity, which is quite thin, becomes attached to connective tissue. In the midst of the spongioblasts round isolated cells appear, which correspond, without doubt, to the germinative cells and to the neuroblasts. Some of them form prolongations, veritable axis-cylinders with a cone of growth that perforates the basal membrane and creeps in between the collagenous fibers of the stroma.

In several of these tumors, besides these embryonic cells, one finds some completely different elements forming ependymal or choroid sheaths, stretches of adult neuroglial tissue and groups of ganglion cells from which emanate real bundles of nerve fibers.

This group of neuro-epitheliomas, with which it is convenient to associate the stephanocyte retinocytoma of Mawas and the esthesio-neuro-epithelioma of Berger, may be distinguished clearly from neurospongiomas.

In comparison with the neurospongiomas, neuro-epitheliomas present both younger and more diverse cellular forms, and it is interesting that these two varieties of tumors are also distinguished by their biologic characteristics. The neuro-epitheliomas are generally tumors with attenuated malignity, but when a neuro-epithelioma assumes the characteristics of active malignity, the characteristics of a neurospongioma will develop more and more. Therefore, the neuro-epithelioma appears somewhat like an evolutionary dysembryoma, while the neurospongioma represents the true cancer of a nerve blastema.

The following tabulation summarizes the relative frequency of the different forms of tumors of the nervous system:

Total number of cases studied, 251

Astrocytomas	119	Gliomas, 178
Oligodendrocytomas	16	
Glioblastomas	43	
Ependymocytomas	14	Ependymomas, 26
Ependymoblastomas	9	
Ependymogliomas	3	
Choroid papillomas	4	
Epitheliomas	3	
Ganglioneuromas	1	
Neurospongiomas	20	
Neuro-epitheliomas	2	
Unclassified tumors	22	

The relatively large number of ependymal tumors observed in this tabulation is explained by the fact that among the tumors examined there occurred a considerable number of intraspinal tumors, and it seems that the percentage of ependymomas is distinctly greater in the spinal cord than in the encephalon.

HISTOLOGIC DIAGNOSIS OF TUMORS OF THE BRAIN

PERCIVAL BAILEY, M.D.
CHICAGO

I shall confine my comments to a discussion of the tumors of the brain substance, leaving to my colleague, Dr. Penfield, the presentation of tumors of the meninges.

The microscopic structure of tumors of the brain is infinitely varied, yet among their kaleidoscopic appearances certain family resemblances may be traced, even though they be as elusive as those of the Dinaric race. There are three great families—the medulloblastoma, the glioblastoma and the astrocytoma—which differ widely in age of onset, site of origin and biologic behavior.

THE TUMORS

The Medulloblastoma.—This is almost exclusively a tumor of the cerebellum of children. Its clinical evolution is rapid, the average length of life of the patient from the onset of the symptoms to death being about fifteen months. It is usually situated in the middle of the cerebellum, but projects into the fourth ventricle. It has an unusual tendency to invade the meninges and spread widely into the subarachnoid spaces, even to the olfactory bulbs in one direction and to the cauda equina in the other. It is a firm, reddish-gray tumor, and is very vascular. Hemorrhages and cystic degeneration are rare.

Microscopically, this tumor is composed mainly of small cells with oval hyperchromatic nuclei. The cells have very little cytoplasm. In teased preparations the cells appear spherical. In fixed preparations they are usually elongated, somewhat the shape of carrots. Mitotic figures are frequent. The cells have a tendency to arrange themselves in such a manner as to leave clear spaces free from nuclei but filled with the cytoplasmic prolongations of the cells. When these spaces are round they resemble the rosettes found in gliomas of the retina, but differ in that there is no cavity. It is better, therefore, to speak of them as pseudorosettes.

While the majority of the neoplastic cells are of the type that I have described, in some of the tumors other types may be distinguished.

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Almost invariably spongioblasts may be found in considerable numbers. They are characterized by having nuclei with a finer network of chromatin, and by denser cytoplasmic prolongations that may be impregnated by methods for neuroglia cells. Sometimes astroblasts and even poorly formed astrocytes may be discovered. In addition, there is occasionally found a cell with a much larger spherical vesicular nucleus, having a heavy nucleolus and very little chromatin. The cytoplasm around this nucleus is stained metachromatically. Although tigroid substance is rarely found in these cells, there can be no doubt that they are neuroblasts, for they are readily impregnated with silver and may be found in all stages of evolution from apolar to multipolar types. I have twice seen tumors in the central part of the cerebellum in children which were composed almost entirely of such differentiating neuroblasts. Where the tumor has invaded the leptomeninx there is a much more abundant connective tissue, so that it is difficult to distinguish the neoplastic cells from those of the hypertrophied leptomeninx. This fact has caused many of them to be classified as sarcomas. Because of the finding of both spongioblasts and neuroblasts apparently differentiating in these tumors I was led to the hypothesis, previously implied by Masson, that the neoplastic cells represent a more embryonic stage of development than either the neuroblasts or the spongioblasts, and likened them to the indifferent wandering cells of the developing central nervous system described by Schaper. I gave these cells the name of medulloblasts and called the tumor a medulloblastoma. The propriety of this name has been disputed, and it was proposed by Hoerner to call them neurospongiomas. Whatever the name finally adopted for this group, the hypothesis of their origin has been confirmed by Masson, Oberling and Wohlwill, all of whom conclude that this group of tumors is one well characterized both pathologically and clinically and is fairly common, constituting about 10 per cent of all gliomas. Occasionally a tumor of similar structure will be found in the cerebral hemispheres.

Glioblastoma Multiforme.—This is also a common type of glioma. It was formerly known as a gliosarcoma. It has been described in great detail by Globus and Strauss under the name of spongioblastoma. It develops almost exclusively in the cerebral hemispheres of adults. It grows rapidly, the average length of the clinical course between the onset of symptoms and the death of the patient being about twelve months. The symptoms often begin abruptly, because hemorrhage and thrombotic softening in the tumor are common.

Microscopically, the tumor is composed of anaplastic neuroglia cells. Most of them are bipolar or fusiform in shape, so that the tumor resembles sometimes closely a spindle cell sarcoma. There are also numerous true neoplastic giant cells. Many of the cells resemble medul-

loblasts, polar spongioblasts, perivascular cells of Andriezen, astroblasts or even small, poorly formed astrocytes. Mitotic figures are numerous. The multiformity of the histologic appearance is due not only to variations in the form of the neoplastic cells, but also to widespread degenerative and reparative changes. Intervascular degeneration is common. The blood vessels are usually abnormal, with thin walls that have often undergone hyaline degeneration. Tortuosity, aneurysmal dilatations, thromboses and ruptures of the vessels are common. In the degenerative areas there is a large amount of fat, and a sort of hyalinization of the cytoplasm that results in the formation of a pseudosyncytium. In teased preparations many clasmatocytes may be identified. This family is a vast one and could doubtless be subdivided histologically, but there would seem to be no practical advantage in doing so since all are equally malignant. They constitute from 20 to 30 per cent of all gliomas.

Astrocytomas.—This is the glioma durum of the classic authors, and is the typical glioma of every textbook. It is a slowly growing, relatively indolent tumor and has a marked tendency to undergo a sort of liquefaction, producing large cysts that practically destroy the tumor. A small mural nodule, however, always persists. These tumors are relatively avascular, and hemorrhages in them are rare. When situated in the cerebellum they cause symptoms in childhood, whereas in the cerebral hemispheres they usually cause symptoms only in adult life. They are composed either of protoplasmic or of fibrillary astrocytes; many of the cells are of transitional type. The time of evolution of these tumors is very long. If the cyst is evacuated and the mural nodule of the tumor removed, the patient may survive indefinitely. The astrocytomas constitute about 30 per cent of all gliomas.

Oligodendrogliomas.—Aside from the great families already outlined there are smaller ones that are also fairly clearly defined. The oligodendroglioma is almost exclusively a tumor of the cerebral hemispheres of adults. It is relatively benign, the average length of life being about sixty-six months. Hemorrhages and cystic degeneration are uncommon, but the tumor is often calcified so that it casts a shadow in the roentgenogram.

Microscopically, the oligodendroglioma is composed of small cells, uniformly distributed. It may readily be confused with the medulloblastoma, but careful examination shows that the nuclei are more spherical, and mitotic figures are rare or absent. The cytoplasm has the form of a ring around the nucleus, often with a clear zone between them. Many of the cells may be impregnated by methods for the oligodendroglia, but most of the cells usually cannot be impregnated by any method. There are found also large cells of indifferent character and some astrocytes.

Spongioblastomas (unipolare et bipolare).—These are also rather indolent tumors and have a predilection for the brain stem, especially in the neighborhood of the optic chiasm. They are grayish, rather avascular, firm tumors. They are common in children and are often associated with peripheral manifestations of von Recklinghausen's disease. They are composed of bipolar and unipolar spongioblasts, which run in long streams with the cells parallel to each other, thus having a superficial resemblance to a peripheral neurinoma. In fact they have been described as central neurinomas.

Astroblastomas.—This small group, usually included with the glioblastomas, is that of tumors occurring almost always in the cerebral hemispheres of adults. They have many of the characteristics of glioblastoma multiforme, but grow more slowly. Their average clinical course extends over a period of more than twenty-eight months. They have a characteristic overgrowth of connective tissue around the numerous blood vessels. The cells nearest the blood vessels have stout vascular processes, which sometimes form veritable palisades along the walls of the vessels.

Ependymomas and Ependymoblastomas.—In the fourth ventricle occurs a firm, rather avascular tumor composed of cells resembling those of the ependyma. The usual tumor of this group is composed of a mosaic of cells with abundant cytoplasm. In most of the cells near the nucleus may be found a group of granules or short rods which stain sharply by methods for neuroglia fibers. These granules are typical of those found in the ependymal cells and are known as blepharoplasts. The cells are often elongated near the blood vessels so that they appear to radiate from the walls of the vessels. These radiated formations are often mistaken for rosettes, but they are distinguished from the rosettes of the retinal gliomas by having a blood vessel in the center instead of a cavity. Depending on the shape of the neoplastic cells, two subgroups may be made which I have called ependymomas and ependymoblastomas.

Pinealomas and Pineoblastomas.—In the pineal body, tumors sometimes develop which resemble closely the medulloblastomas, but may be distinguished by the fact that the cells are larger, have more cytoplasm and are round. The nuclei are also larger and more vesicular. These cells may lie in a more or less homogeneous mass containing scattered blood vessels; the tumor is then called a pineoblastoma. In others there is a considerable overgrowth of connective tissue which divides the neoplastic cells into lobules. The connective tissue is infiltrated with lymphocytes. This association of lymphoid tissue and embryonic pineal cells is characteristic of the more adult tumor called the pinealoma.

Ganglioneuromas.—Rarely, in the brain there occurs a tumor that resembles closely the ganglioneuroma of the peripheral nervous system. It is characterized by the presence of numerous neoplastic nerve cells separated by neuroglia or neurinomatous tissue. This tumor occurs usually in the neighborhood of the tuber cinereum, but has been found in the cerebellum and in the medulla oblongata.

Neuro-Epitheliomas.—In the retina occurs a peculiar type of gliomatous tumor called a neuro-epithelioma. It is characterized by the presence of numerous small cavities surrounded by the columnar bodies of the neoplastic cells. These formations are known as rosettes, and the cells that form them resemble primitive spongioblasts. At their inner ends they bear cilia and blepharoplasts. Such tumors are excessively rare in the brain, but I have seen three or four typical cases.

COMMENT

From the brief characterizations given it can be seen that there occur in the brain fairly well defined groups of tumors, each of which has its own peculiarities that enable it to be recognized. Of course, there are numerous mongrels that cannot be affiliated with any of these families. Perhaps 12 or 15 per cent of the gliomas cannot be affiliated with any of the groups.

It is obvious to any one who has had to deal with tumors of the brain that they do not all behave alike. It was because of a desire to understand this variation of behavior that the attempt was made to classify them, a proper classification being the first step toward the understanding of any group of natural phenomena. Against the classification that I have adopted, many objections have been urged. I have no time to notice more than a few of them.

In the first place it has been urged that the structure of gliomas is so varied that any attempt to classify them is futile. I have never maintained that all gliomas could be classified in this way, but many gliomas can be easily recognized as belonging in the groups that I have described. When a series of similar tumors is collected one can, by making a synthesis, gain some idea of the behavior of the group as a whole.

Second, it has been said that the structure of gliomas varies so much in different parts that it is impossible to give a single simple name to any glioma. This is not strictly true. Some gliomas vary a great deal; others do not. The situation is the same with tumors of the connective tissue. Everyone knows that the pathologist may be obliged to diagnose osteochondrofibrosarcomas. But this does not alter the fact that one may encounter a fibroma or a chondroma of fairly pure structure, and the isolation and description of these types are justifiable for purposes of analysis, as well as for the purposes of description and teaching.

Third, it has been urged that this method of classification is based on an embryogenic theory, namely, that the tumors develop from cells arrested at a certain embryologic stage of development. I have never maintained any such theory for all gliomas, and it is only probable, as far as I can see, in the case of the medulloblastomas. The most that I have done is to give names to the tumors chosen from the terminology of the histogenesis of the nervous system because the cells of the tumors seem to resemble in their structure these embryologic forms.

Fourth, it has been urged that since more than 50 per cent of the gliomas fall into the three large groups of medulloblastoma, glioblastoma multiforme and astrocytoma, the other groups are superfluous. This suggestion cannot be taken seriously. It is absurd to argue that because an oligodendroglioma rarely occurs in the central nervous system it ought to be classified with the astrocytomas.

Fifth, it has been remarked that the classification of gliomas is useless indoor sport. The study of any group of natural phenomena needs no justification. Some people collect butterflies, others beetles. I collect tumors of the brain and classify them, and find the process sufficiently interesting to repay me for the time I spend at it.

Sixth, I might mention that in a recent review of the German edition of the monograph that I published in collaboration with Cushing, Herr Bielschowsky remarked that there is, after all, nothing particularly new in all this. I should certainly agree with that statement. Perhaps the only thing that can be considered new is the creation of a rather small group of tumors composed largely of oligodendroglia and of their forerunners the oligodendroblasts. But nobody can deny that this group of tumors was badly in need of study, and I am sure that in the near future ideas concerning them will be considerably clarified.

It has been stated also that the histologic nature of the glioma is of no importance for treatment, the only safe guide being the gross appearance and relationship of the tumor. I am convinced, however, that the histologic nature of the tumor is of considerable practical importance both for the treatment and for establishing the prognosis.

It seems to me that there are three times when one would like to know the histologic nature of a tumor with which one is dealing:

1. It should be known before operation, because the operability of the tumor and the method of attack, I still believe, should depend to a certain extent on the histologic structure of the tumor. This is rarely possible to predict, up to the present time, in the case of tumors of the nerve tissue itself. Yet certain things have been learned. In childhood a certain clinical syndrome, now known generally as the syndrome of the vermis, accompanied by signs of intracranial tension, means one of two gliomas almost invariably, either a medulloblastoma or an astro-

cytoma. It has been learned also that when symptoms of a tumor develop in the cerebral hemispheres in adult life, particularly at middle age or later, the chances are overwhelmingly in favor of finding a malignant, rapidly growing and infiltrating glioma, formerly called a gliosarcoma and now spoken of as a spongioblastoma or a glioblastoma multiforme. It is known that when the vision of a child with peripheral manifestations of generalized neurofibromatosis begins to fail, there is likely to be found a glioma of the optic chiasm of the type known as a spongioblastoma (unipolare et bipolare). It is known also that when symptoms of a tumor in the cerebral hemispheres coexist with a calcification visible with the x-rays one is likely to find a slowly growing type of glioma, in most cases an oligodendroglioma. These are meager results, it may be said, of such a long and arduous study.

There is, perhaps, one other more direct method of determining something of the nature of a tumor of the central nervous system before operation, and that is the method of puncture of the brain proposed by Pfeiffer. I have had no experience with this method. If I were sure that I could distinguish between different varieties of gliomas by the tissue removed in this way, I might be willing to use it, although heretofore the fear of intracranial hemorrhage has deterred me. Its use simply to diagnose a tumor is not necessary, since the same diagnosis may more readily be made by ventriculography.

2. When the surgeon discloses a tumor at operation I still believe that there are cases in which his attack should depend on the histologic nature of the lesion, and I am rarely sure enough of the nature of a glioma from the gross appearance to be willing to base my therapeusis thereon alone. I know well that there are neurologic surgeons in the United States who do not agree with me. Recently, one well known neurologic surgeon in my presence disclosed a midline cerebellar tumor in a child. As the patient's condition was precarious, he closed the wound, intending to remove the tumor at a second operation. I told him that under similar circumstances I should have made a biopsy, and if I had found the tumor to be a medulloblastoma I should have saved myself another morning's work. He replied that he would go back and attempt to remove the tumor, whatever its histologic nature might be. Yet to my knowledge no one has ever succeeded in removing a medulloblastoma in this situation so completely that the symptoms did not recur within a few months. And I have been able to prolong the lives of such children with roentgen radiation just as successfully as this surgeon has by operative removal.

There are two methods of determining during operation the nature of the tumor with which one is dealing, apart from the gross appearance. One is the method of supravital examination recently reported on by Dr. Louise Eisenhardt. I have had several years' experience

with this method, and I have not been able to become sufficiently expert to be willing to base my diagnosis on this method alone. It is possible in this way to distinguish between a meningeal tumor and a glioma, for example, but I find plenty of difficulty in distinguishing the different types of gliomas from each other with all of the resources of microscopic technic at my command. The other is the method of frozen sections, and this to my mind is still the most reliable, for the differentiation of the types of gliomas demands a knowledge of the architectural arrangement of the cells as well as of the structure of the individual cells.

3. After the operation, either from operative specimens or from the necropsy, one obtains material that is useful for microscopic study. It has no longer much immediate practical value, except, perhaps, in the case of the operative specimen for making a prognosis. But it is still useful and interesting from a purely scientific standpoint, and although one may make a fairly shrewd guess, after a certain amount of experience, from a section stained simply with hematoxylin and eosin, I have found that specific staining and impregnation methods are necessary for any finer histologic study. For this purpose I employ three fixatives, either Zenker's or Bouin's fluid, a diluted formaldehyde solution ("solution of formaldehyde U.S.P." 1, water to make 10) and Cajal's formaldehyde-bromide solution. Other fixing solutions are rarely needed. It is then necessary to make sections for different purposes by the freezing method, by the paraffin method or by the celloidin method. The details of all these various procedures will be found in my monograph on tumors of the glioma group.

The problem of how to treat tumors developing from the substance of the brain is one of the most knotty in all medicine, and if the histologic studies that I have made should prove to be of assistance in the untangling of this problem I shall be glad; if not, I shall still have had the enjoyment of studying them.

TUMORS OF THE SHEATHS OF THE NERVOUS SYSTEM

WILDER PENFIELD, M.D.
MONTREAL, CANADA

In this short space it is possible only to outline certain important conclusions in regard to the histology of the tumors of the sheaths of the nervous system without including the detailed discussion that they deserve. But I may take this opportunity of apologizing to those other students of this subject whose work is not cited here, however conscious I may be of my debt to them.

From the point of view of neurology and neurosurgery it is of the utmost importance that one nomenclature be adopted throughout the world, and that the temptation of substituting new terms for old ones be resisted unless the new terms express an important change in the conception of the neoplastic entity involved. I shall deal with the primary tumors of the meninges and nerve sheaths.

TUMORS OF THE MENINGES

1. *Meningeal Fibroblastoma* (Psammoma, Dural Endothelioma, Meningioma).—These tumors form a well recognized entity. It is entirely unnecessary to discuss their formation by ingrowths of arachnoid into the dura (Schmidt, 1903). It is unnecessary to point out that they resemble arachnoid granulations, forming cellular whorls histologically (fig. 1), and that they are encapsulated although they occasionally infiltrate the overlying bone, producing osteogenesis as they do so. The question to be discussed is one of identity and of terminology.

The term dural sarcoma is an obvious misnomer, as it would suggest greater malignancy than these tumors show. Dural endothelioma bears the sanction of time-honored usage, but the tumor is not an endothelioma in the accepted meaning of the term, and there is no separate order of meningeal endothelial cells. Psammoma, the name given these tumors by Virchow, is satisfactory for those specimens which form sand or corpora amylacea in large quantities, but it is inapplicable to at least half of the tumors, and makes no statement as to their nature.

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The latter criticism may be leveled at meningioma, a blanket term suggested by Cushing, as it also avoids the issue of identification. Because of its simplicity, however, and the distinction of its sponsor, the term meningioma has gained wide popularity (Bostroem and Spatz, 1929). This term, if it be accepted in the broadest sense to mean any tumor arising in the meninges, is admissible. It then includes sarcomas, hemangiomas and even lipomas that arise in the meninges, a point of view recently adopted by Bailey, Cushing and Eisenhardt (1928).

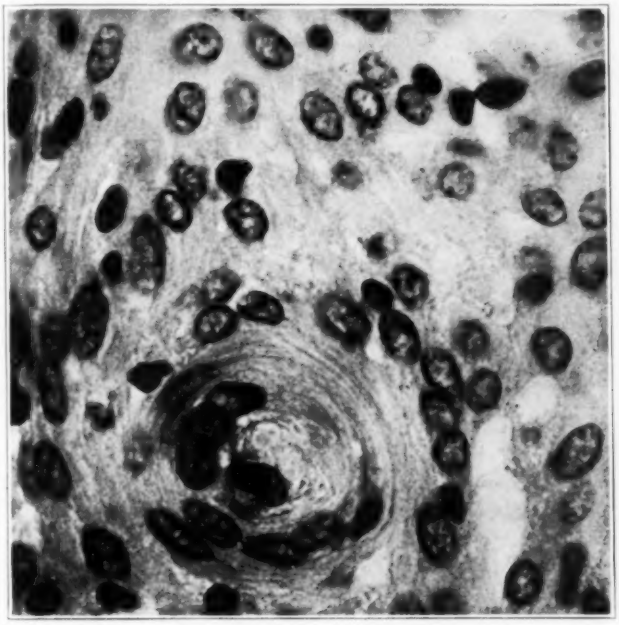

Fig. 1.—Meningeal fibroblastoma from the spinal canal. Note the fibroglia fibrils in the whorl. Hematoxylin and eosin stain; reduced from × 1,320. (After Penfield, 1927.)

Bailey and Bucy (1931) still more recently have separated the tumors of the meninges into nine subdivisions. Theoretical justification for such elaboration is not found wanting. But is it expedient thus to complicate a relatively simple problem? These authors include angioblastomas, melanoblastomas, lipomas and diffuse sarcomas of the pia in this classification, four tumor entities that are of importance and that may rightly be included under the heading of meningioma. But they do not belong to that group of neoplasms formerly designated as "dural endothelioma." The remaining five subdivisions suggested by these authors, i. e., mesenchymal, meningotheliomatous, fibroblastic,

psammomatous and osteoblastic meningiomas, do belong to this group, and it may be observed in passing that the possibility of such a classification of the meningeal tumors is eloquent evidence of the connective tissue nature of the meninges as is pointed out by the authors themselves.

For the purpose of analysis of the meningeal fibroblastomas, these subgroups will serve. Whether a particular tumor falls into one or the other of the groups mentioned depends only on its degree of differentiation. In my experience the more slowly growing tumors are the more differentiated; that is, more of their cells show the elaborated characteristics of meningeal fibroblasts, forming collagen and fibroglia

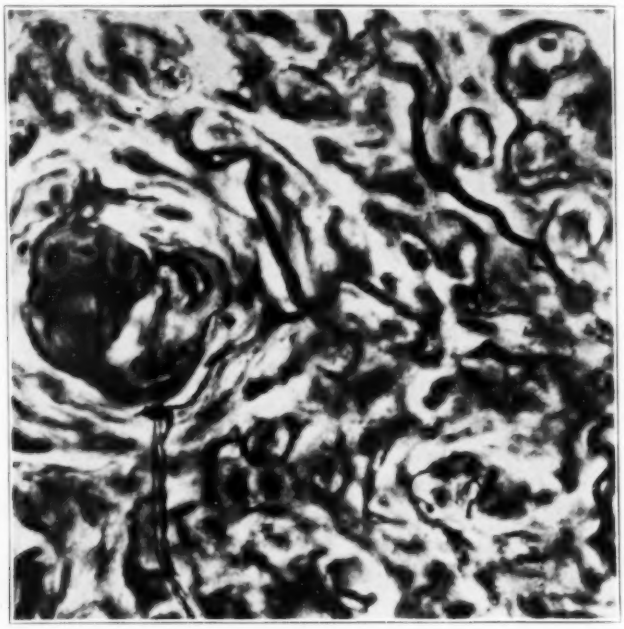

Fig. 2.—Meningeal fibroblastoma; same case as in figure 1. Note the size and arrangement of the collagen fibrils. Silver carbonate connective tissue strain; reduced from × 1,320.

and permitting the deposit of corpora amylacea, a trait particularly characteristic of meningeal cells in the pacchionian granulations and in the invaginations of pia-arachnoid into the choroid plexuses. The collagen that is formed by these tumors (fig. 2) is so characteristically different from the collagen formed in tumors arising from nerve sheaths that an adequate collagen stain is invariably sufficient to indicate into which of these two common types a particular example falls.

The less differentiated tumors, which may be said to resemble "meningothelium" or even "meningeal mesenchyme," grow somewhat

more rapidly, in my experience. All of these types show histologically some of the tendency characteristic of meningeal cells to wrap themselves about almost any structures with which they come into contact and thus form cellular whorls. But all these histologically divided tumors are biologically similar. They may recur locally if not completely removed, and they may invade the overlying bone in an altogether characteristic fashion.

Finally, it is apparent that one is dealing with one tumor entity. The type cell, wherever sufficiently differentiated, has the characteristics of a fibroblast. It retains the traits or traditions peculiar to fibroblasts of the meninges. Therefore, Mallory (1920) named this tumor arachnoidal fibroblastoma, and agreeing with Mallory, I also called it fibroblastoma (1927, 1932), but substituted *meningeal* for arachnoidal, as occasional tumors have no gross attachment to the arachnoid.

The fact that meningeal fibroblastomas vary to a certain extent in histologic picture does not necessitate subdivision. A similar range of cell differentiation is seen in various parts of the normal meninges themselves if one compares the undifferentiated arachnoidal cell groups with the pacchionian granulations and the well differentiated dura mater. In the diagnosis of a carcinoma derived from a gland one does not demand reproduction of the detail of the gland in every field. Extended search may be required before the neoplastic cells are seen to betray traits peculiar to the gland in question. Can one not similarly accept the meningeal fibroblastoma, although it may not be possible to stain fibroglia fibrils in every cell? To the diagnosis of meningeal fibroblastoma may be added, if desired, the qualification of "little differentiated," "psammomatous," etc. Further subdivision and reclassification may be tempting but are not expedient.

The suggestion of Oberling (1922) that the term meningoblastoma be adopted for these tumors is based on his conclusion that some of the examples in this group of tumors are histologically gliomas, sarcomas, epitheliomas, etc. Critical study of the cytology alone can answer such a contention. During the study of neuroglia by various methods for many years I have never found a cell in a meningeal tumor that could be considered glial, provided the stain was satisfactory.

Space does not permit a discussion of the origin of the meninges. There seems to be no reason to depart from the point of view of His, of Koelliker and Weed (1932). Occasional heterotopia of neuroglial tissue in the meninges is not an argument against their mesodermal nature (Buckley and Deery, 1929).

2. *Meningeal Sarcoma.*—The melanoblastomas, lipomas and angioblastomas of the meninges require no discussion. They may be understood by a knowledge of those same tumors arising in other structures.

However, sarcoma of the dura must be mentioned, as these tumors show a structure sometimes reminiscent of the meninges and of the meningeal fibroblastomas. Biologically, they resemble sarcomas of this type in other regions, being locally malignant (Craig, 1927) and eroding

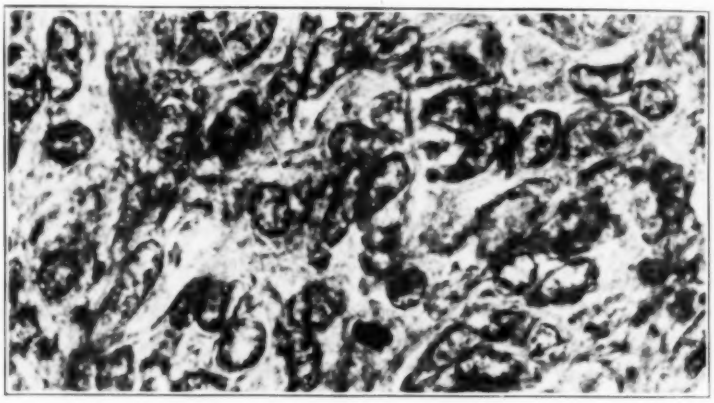

Fig. 3.—Sarcoma of the cranial dural mater which penetrated the skull by erosion without involving it. Note the mitotic figure. Hematoxylin and eosin stain. (After Penfield, 1932.)

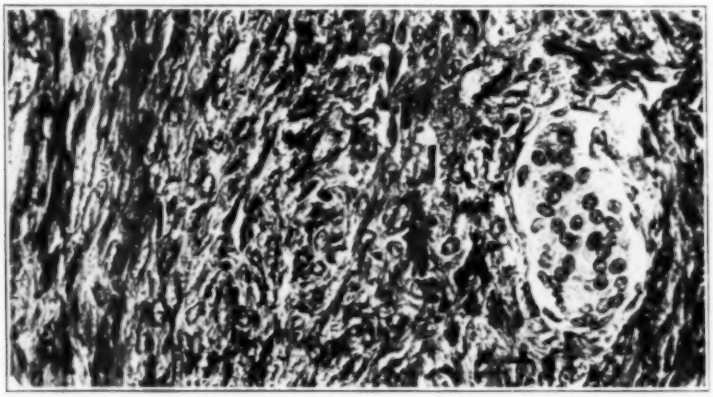

Fig. 4.—Sarcoma; same case as in figure 3. Note the collection of cells with arachnoidal arrangement. Hematoxylin and eosin stain. (After Penfield, 1932.)

the overlying bone instead of producing osteogenesis within it (Penfield, 1923).

They grow rapidly and contain mitotic figures (fig. 3). The extradural sarcoma, which so frequently produces spinal compression, arises in many cases from the dura itself, as is betrayed by its histologic structure. This tell-tale of the origin of these tumors may be found

in scattered areas where groups of cells are found arranged in tufts or islands resembling undifferentiated arachnoidal tufts (fig. 4).

Sarcoma of the leptomeninges, also a rare neoplasm, metastasizes through the cerebrospinal fluid as is to be expected. It behaves in that sense like some of the gliomas and like hemangioblastomas when these tumors have invaded the leptomeningeal space.

TUMORS OF THE NERVE SHEATH

1. *Perineurial Fibroblastoma* (Neurinoma, Schwannoma, Solitary Neurofibroma, Cerebellopontile Angle Tumor).—To enumerate only a few of the synonyms is to bring clearly to mind the tumor entity under discussion. Again the problem is one of terminology and identity.[1]

These tumors do not contain nerve fibers. The mistaken belief that they did do so led Verocay to call them neurinomas. They do not contain neuroglial elements, to the best of my belief after exhaustive study by means of special neuroglia methods. The type cell is not the Schwann cell but the connective tissue perineurial and endoneurial cell, as shown by the following facts. The tumor cells form fibroglia, collagen fibrils and elastic tissue (Mallory, 1930). The outstanding histologic characteristic of these tumors is the presence in them of long parallel hairlike fibrils which stream together like hairs in a brush (fig. 5). They are not nerve fibrils. They are the architectural support without the nerve. They are reticulin fibrils staining with the same specific stains used for reticulin elsewhere.

If one examines these reticulin fibrils in a normal nerve, they are seen to run in the endoneurium to the point where the nerve enters the spinal cord or medulla (fig. 6). There these hairlike fibrils pass off continuously into the leptomeninges, showing the identity of their structure with the collagen structure of the leptomeninges. The Schwann cells, which seem to be analogous to neuroglia, could hardly be expected to form fibrils of this sort which bear no resemblance to neuroglia fibrils.

The palisading of the nuclei characteristic of these tumors takes place because of the presence of sheaves of these peculiar hairlike reticulin fibrils which crowd the nuclei to either end of the sheaves (fig. 7).

2. *Peripheral Gliomas.*—These tumors do occur, although they are extraordinarily rare. They arise from the cells of the sheath of Schwann or their precursors, but do not in any way resemble perineurial fibroblastomas. They resemble little differentiated gliomas. If any tumors are to be called schwannomas, these should be.

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1. An extended discussion of the excellent work on this subject by Masson, Roussy, Lhermitte and Cornil, Antoni, Mallory, van Wagenen and others may be found in Penfield, 1932 (see bibliography).

Fig. 5.—Perineurial fibroblastoma of the eighth nerve. Note the bundles of parallel reticulin fibrils. Laidlaw's connective tissue stain.

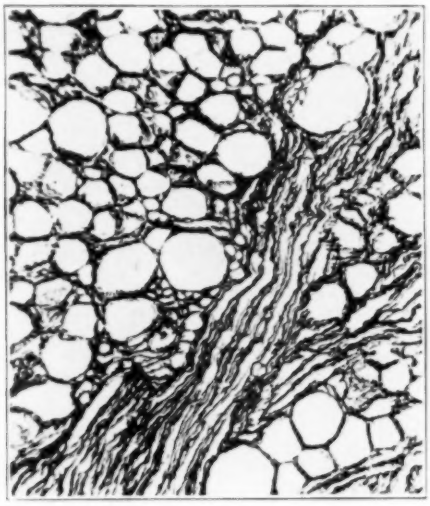

Fig. 6.—Reticulin fibrils in posterior spinal root leaving ganglion: Laidlaw's connective tissue stain; somewhat higher magnification than in figure 5.

The peripheral glioma described here (fig. 8) shows rosettes and a coarse collagen stroma.[2] The tumor arose in the ulnar nerve. It contained numerous mitotic figures, and eventually metastasized and killed the patient ten months after its first appearance. It should be called a neuro-epithelioma. Theoretically, more benign gliomas may also be expected to form on peripheral nerves, but I have never been fortunate enough to see an example.

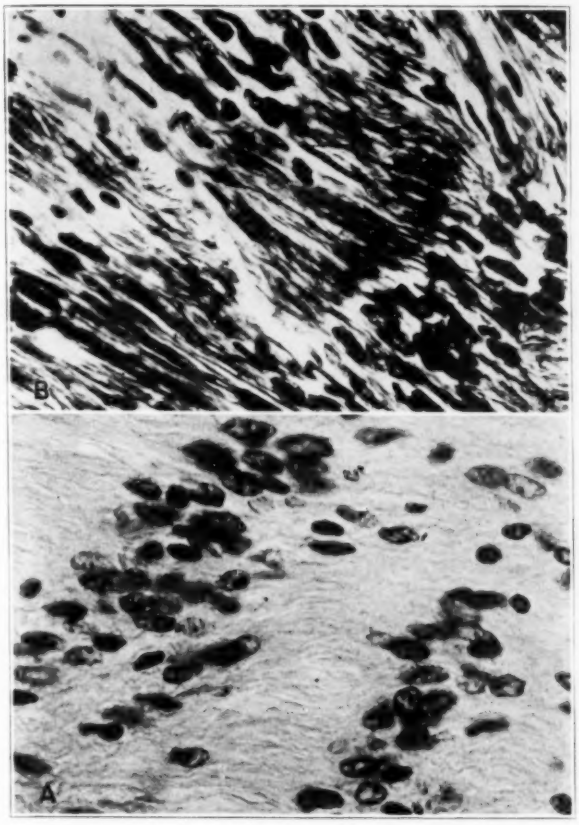

Fig. 7.—Perineurial fibroblastoma: *A*, palisading of nuclei; hematoxylin and eosin stain. *B*, reticulin fibrils lying between the palisading nuclei; silver stain.

3. *Neurofibroma of von Recklinghausen.*—The use of the name of the man who gave the first clear description of these tumors identifies the neoplasm sufficiently. One recognizes neurofibromatosis as a familial disease of a diffuse character in which meningeal fibroblastomas,

2. Dr. A. P. Stout, of New York, my former colleague, permitted the use of this case.

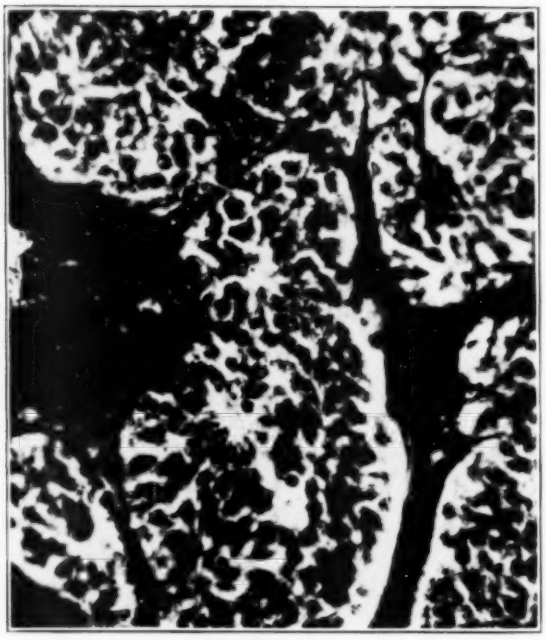

Fig. 8.—Neuro-epithelioma of the ulnar nerve. Note the collagen stroma and the tendency of the tumor cells to form rosettes. (After Penfield, 1932.)

Fig. 9.—Neurofibroma of the peripheral nerve. Note the disorderly arrangement of the cells.

gliomas and sarcomas may on occasion be encountered. But the commonest characteristic of this disease is the presence on the nerves of multiple tumors whose histologic structure suggests a connective tissue reaction of some sort. Typical perineurial fibroblastomas (Antoni's pure neurinomas) may be encountered or may be found as part of one tumor, but the typical neurofibroma contains reactive connective tissue (fig. 9) and occasional nerve fibers belonging to the parent nerve (Antoni's mixed structure). The presence of nerve fibers in the tumor (fig. 10) shows at once that one is dealing with neurofibroma and not perineurial fibroblastoma. In the latter tumor the nerve fibers of the

Fig. 10.—Neurofibroma on the cauda equina in a case of von Recklinghausen's disease. Gros-Bielschowsky neurofibril method. This was an extremely small nodule. The nerve can be seen entering the tumor at the left upper corner. (After Penfield and Young, 1930.)

parent nerve will be found plastered about the tumor in the capsule, not entering the neoplasm.

CONCLUSION

From a practical point of view there are only three common types of tumors of the sheaths of the nervous system, all encapsulated and benign. Neurofibroma, least common and a product of von Recklinghausen's disease, contains nerve fibers in its mixed histologic structure. The meningeal fibroblastoma has a tendency to whorl formation of nuclei, and the perineurial fibroblastoma a tendency to palisade arrangement.

This is not enough to distinguish the last two from each other in difficult cases. A careful reticulin stain, such as one of the modifications of the Bielschowsky stain (Mallory and Parker, 1929; Laidlaw, 1930) will betray at once the tumor derived from the nerve because of the easily recognized hairlike fibers. The distinction of meningeal from perineurial tumor then becomes simple and certain.

Derived from the meninges, two types of tumor should be recognized: meningeal fibroblastoma, a benign tumor with certain unusual characteristics, and meningeal sarcoma, which is less benign and resembles sarcoma elsewhere.

Derived from the nerve sheath, perineurial fibroblastoma is an easily recognized, encapsulated tumor found most frequently on the acoustic nerve and spinal roots. Peripheral gliomas derived from the neuroglial elements in a nerve, although extremely rare, resemble the more malignant central gliomas. The neurofibroma of von Recklinghausen's disease is more like a focal increase in the curious process that takes place diffusely throughout the length of the nerves in such cases.

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VENTRICULOGRAPHY AND ENCEPHALOGRAPHY

THEIR VALUE IN THE LOCALIZATION AND TREATMENT OF INTRACRANIAL LESIONS

FRANCIS C. GRANT, M.D.
PHILADELPHIA

A precise diagnosis of the exact character and position of a lesion of the brain is often difficult. Clinical symptoms may be scanty or misleading, and even after a conclusion is reached as to the real nature of the disease the question of proper therapy must be decided. Many intracranial conditions are not amenable to direct treatment in the light of present knowledge. The protean manifestations of cerebral syphilis can be benefited if treated in time. Surgery has shown in the last twenty-five years how much may be accomplished by prompt exploration when a tumor, an abscess or a posttraumatic scar is present. Cerebral syphilis and surgical lesions in general, however, are the only intracranial conditions that can be materially improved by methods now available.

Since surgery provides the readiest means of relief for certain conditions, an early recognition of the proper indications for operative intervention is important. It is in the prompt determination as to whether or not an intracranial lesion can be benefited by surgical intervention that the recently introduced methods of diagnosis by ventriculography and encephalography are especially valuable. By their use, not only the character but also the position of the lesion is shown, which is a great aid to the surgeon in the proper planning of the operative approach if a direct attack appears to be indicated. Furthermore, in certain nonsurgical conditions, the insufflation of air seems of itself to have a definite therapeutic value.

In an attempt to determine the usefulness of these procedures in the differential diagnosis and localization of lesions of the brain and

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From the Neurosurgical Clinics of the University Hospital and the Post Graduate Hospital of the University of Pennsylvania.

Dr. W. G. Spiller and Dr. T. H. Weisenburg gave me the privilege of using material from their neurologic clinics, and Dr. H. K. Pancoast and Dr. G. E. Pfahler helped me develop the radiologic technic and interpret the encephalographic findings.

their therapeutic effect on the symptoms accompanying such conditions, a series of 325 encephalograms and 160 ventriculograms has been analyzed.

Dandy [1] and Bingel [2] have shown that the fluid in the subarachnoid spaces and ventricles of the brain can be safely withdrawn and replaced by air, and that on an x-ray film the air throws a shadow that can be readily distinguished from that produced by the cranial bones. The size, shape and position of the cerebral ventricles and the various arachnoid cisternae and spaces are accurately outlined. By the use of this method, therefore, it is relatively simple to determine whether or not the lesion revealed demands surgical relief, and if so, to plan the operative procedure with accuracy.

Three methods exist for the removal of fluid and the insufflation of air: lumbar puncture, occipital puncture and direct tap of one or both lateral ventricles. Curiously enough, there has crept into the literature a difference in the terminology describing these methods, although the results with each are practically identical. "Encephalography" means that the lumbar or suboccipital route has been used; "ventriculography," that the skull has been trephined and air introduced directly into the ventricles. This difference in nomenclature probably arose from the fact that by ventriculography the lateral, third and fourth ventricles are more apt to be completely filled, whereas the subarachnoid space frequently contains little or no air, while in encephalography the subarachnoid spaces and cisternae are well shown and the inferior and posterior horns of the lateral ventricles may not be clearly outlined.

As far as the experience of my associates and myself is concerned, lumbar encephalography and ventriculography are the two methods practically always used. Suboccipital encephalography has been employed very rarely, because we do not concede, as Eskuchen,[3] Goette [4] and Ginzberg [5] claimed, that it is as safe as the lumbar route, that it produces a better filling with air of the cerebral spaces and consequently more satisfactory x-ray films, or that it is less strain on the patient. This method certainly should never be undertaken when increased intracranial pressure is present.

No matter what technic is used in lumbar encephalography or ventriculography, the most important factor to be kept in mind at all times in obtaining x-ray films of real diagnostic worth is that all the fluid

1. Dandy, W. E.: Ann. Surg. **68**:5, 1918; Surg., Gynec. & Obst. **30**:329, 1920.

2. Bingel, A.: Deutsche med. Wchnschr. **47**:1492, 1921; Med. Klin. **17**:300 and 608, 1921.

3. Eskuchen, K.: Ergebn. d. inn. Med. u. Kinderh. **34**:243, 1928.

4. Goette, K.: Deutsche Ztschr. f. Nervenh. **110**:9, 1929.

5. Ginzberg, R.: Arch. f. Psychiat. **89**:711, 1930.

that can possibly be removed should be withdrawn. It is not necessary to replace an equal amount of air, provided this is done. Fluid remaining in one horn of a lateral ventricle or in the cortical or basal subarachnoid spaces, however, will prevent access of air to this region and suggest the presence of a lesion. Rotation of the head, coughing, straining and jugular compression should be employed to assure the escape of all the fluid obtainable.

Broadly considered, intracranial lesions produce either symmetric or asymmetric changes in size, shape and position of the shadows of the ventricles and arachnoid spaces. Such changes are particularly well exemplified by the effects produced by an expanding lesion, such as a tumor, an abscess or a chronic subdural hemorrhage. A tumor in one cerebral hemisphere always produces obliteration of, or a filling defect in, the lateral ventricle of that hemisphere, while the size and contour of the other lateral ventricle may not be changed, nor the cortical channels much affected. Schuster [6] reported a case in which the tumor was situated on the same side as the larger lateral ventricle, but we have never noted a similar occurrence. However, a deviation from the normal air shadow of the lateral ventricle must be taken into consideration in localizing a lesion. Apparently, not infrequently the posterior horn may be short and blunted or even entirely lacking, as Penfield [7] has pointed out. This normal defect in the ventricular outline may easily suggest the presence of a lesion, but unless the patient is already blind, the changes in the visual fields will help to determine whether or not the absence of the posterior horn is due to a tumor. Furthermore, as the exploring cannula must pass through this region in reaching the ventricle, a change of resistance on encountering the tumor will reveal its presence. A supratentorial tumor lying in the midline between the cerebral hemispheres, and any subtentorial lesion, by interfering with the circulation of the cerebrospinal fluid, causes a symmetrical dilatation of all the ventricular spaces above the point of obstruction, resulting in a greater or lesser degree of internal hydrocephalus. The arachnoid spaces may or may not be affected, depending on the amount of intracranial pressure. When lesions affect particularly the cortical and basal subarachnoid spaces, this classification holds in the main. These channels may be dilated or obstructed symmetrically over both hemispheres or only on one side. But cortical atrophy or "arachnitis" may be very marked over one or both hemispheres, unaccompanied by any changes in the size, shape or position of the lateral ventricles.

Precisely what is meant by "arachnitis" must be clearly understood. "Arachnitis" is a term coined by the radiologist to mean a lack of

6. Schuster, J.: Klin. Wchnschr. **4**:552, 1925.

7. Penfield, W.: Cerebral Pneumography: Its Dangers and Uses, Arch. Neurol. & Psychiat. **13**:580 (May) 1925.

filling with air of the hemispheral or basal arachnoid channels. Presumably the failure of the air to replace the fluid in any region is due to widespread inflammatory adhesions, a meningitis, preventing the interchange between fluid and air. Actually, it may mean nothing of the kind. In several instances, an operative exposure over an area of "arachnitis" showed an excess of fluid in the cortical arachnoid spaces lying under a normal-appearing arachnoid membrane. In other cases, in plates taken twenty-four hours after the first encephalogram or on repeating the injection of air, the channels apparently blocked off were seen to be well filled. Either the block preventing the replacement of fluid by air was low down at the base, say at the point where the arachnoid channel of the sylvian fissure leaves the basilar cistern, so that although the cortical spaces on visual inspection appeared normal, the fluid could not escape, or, because of some unknown hydrodynamic cause or fault in technic in withdrawing the fluid, the area in question was not drained. But the point to be emphasized is that "arachnitis," while it suggests inflammatory adhesions, simply means lack of drainage and failure of the air to reach a certain region from some cause or other which may or may not be due to a demonstrable pathologic process.

As Dandy was interested in neurosurgical problems and developed ventriculography for the localization of tumors of the brain, this method was at first used almost exclusively in this country. Furthermore, in neurosurgical clinics for the most part there is a healthy fear of performing a lumbar puncture in the presence of increased intracranial pressure. Hence, encephalography has only lately come into prominence, since the neurologist found it could be carried out with perfect safety if spinal tension was not markedly increased. Consequently, it has been used promiscously in a great variety of intracranial conditions. But the principal value of encephalography to the neurosurgeon consists in the fact that its use affords an easy method of confirming an opinion based on the history and clinical observations that in a given case no indication for surgical intervention exists.

VENTRICULOGRAPHY

The chief indication for ventriculography is increased intracranial pressure, the cause for which cannot be accurately localized. Owing to the technical difficulties involved in this procedure, its use has been limited practically entirely to patients suspected of having a tumor of the brain. No claims as to its therapeutic value have been advanced. In some instances very large tumors produce absolutely no reliable neurologic signs to define their position. At other times, although it is obvious in which cerebral hemisphere the tumor lies, it is difficult to

be certain whether its position is anterior or posterior. Since a successful attack on such a lesion depends in great measure on the proper placing of the operative approach, the value of the accurate information afforded by a ventriculogram is obvious.

The technic of ventriculography has been described elsewhere [8] and needs no repetition here. As a result of considerable experience, three important points should be emphasized: (1) Always tap both ventricles; (2) be certain that the drainage of fluid is as complete as possible; (3) operate as soon as localization can be made from the x-ray films.

Both lateral ventricles should be tapped in every instance for, thus, drainage of the fluid is more complete and any abnormalities in the size, shape and position of the ventricular system as depicted on the films are due to the tumor and not to undrained fluid. All the errors in localization we have made have been due to incompletely removed fluid simulating a filling defect due to a tumor. Whether or not the lesion obstructs the foramina of Monro may be determined by bilateral tap and the injection of a dye—methyl blue—into one ventricle and its recovery from the other.

Furthermore, if both ventricles are tapped and communicate, after all the fluid that will escape spontaneously has been obtained, the remaining fluid is siphoned from one needle and air enters the ventricles through the other. By rotation of the head and repeated jugular compression, all the fluid is thus replaced by air without increasing the intracranial pressure or actually injecting any air. Lastly, and most important of all, by a bilateral tap a fair idea of any abnormality in the position of the lateral ventricles may be obtained, while separate measurement of the fluid escaping from each needle affords a good estimation of their comparative size. The trephine openings must be placed accurately on either side of the midline in the same relative position to the points at which the lateral ventricles are to be entered. If, through properly placed incisions, one ventricle is punctured at the usual depth with the needle in the normal planes, whereas the other is found shifted in position and at a greater distance from the surface or cannot be tapped at all, it is suggestive evidence of variation in its size due to encroachment by a tumor. If the fluid escaping from one ventricle is much greater in amount than that obtained from the other, this again argues for disproportion in their relative size.

A cerebral hemispheric tumor, as has been noted, in the great majority of instances impinges on and changes the size, shape and position of the corresponding lateral ventricle. Hence, by this method

8. Grant, F. C.: Surg., Gynec. & Obst. **46**:689, 1928. Gardner, W. J., and Frazier, C. H.: Ventriculography Without Air Injection, J. A. M. A. **93**:193 (July 20) 1929.

of bilateral trepanation and ventricular estimation [9] it is frequently possible to determine which cerebral hemisphere harbors the tumor without the necessity of injecting air (table 2). If an accurate neurologic examination shows that none of the actively responding cortical centers of the hemisphere under suspicion are involved, the tumor must therefore be in a silent area, such as the right frontal or temporal regions.

TABLE 1.—*Results with Ventriculography; Analysis of One Hundred and Sixty Cases*

I. Localized by ventriculography			93
Percentage of all cases	58.1		
A. Confirmatory of neurologic signs		45	
Percentage of all cases	28.1		
Percentage of all localized cases	48.4		
B. In absence of neurologic signs		48	
Percentage of all cases	30.0		
Percentage of all localized cases	51.6		
II. Localization probably correct but unverified			32
Percentage of all cases	34.4		
III. Tumors ruled out by ventriculography			5
Percentage of all cases	3.1		
IV. Operative errors due to ventriculography			3
Percentage of all cases	1.8		
V. Errors in technic			17
A. Insufficient air		10	
B. Inability to tap ventricles		5	
C. Bad films		2	
Percentage of all cases	10.6		
VI. Mortality due to ventriculography			10
Percentage of all cases	6.2		
Total			160
VII. Tumors localized by ventriculogram alone and successfully removed			21
Percentage of all cases	13.1		
Percentage of all localized cases	22.6		

TABLE 2.—*Results with Ventricular Estimation in Fifty-Two Cases* *

	Cases	Percentage
I. Ventricular asymmetry found	39	75
A. Tumor verified on side of smaller ventricle	35	90
B. Probably correct but unverified	4	10
II. Ventricular symmetry found	13	25
A. Tumor verified in posterior fossa or third ventricle	9	70
B. Probably correct but unverified	4	30
III. Mortality	1	1.9

* In every case it was possible to reach one or the other lateral ventricle.

If, however, the ventricles are both normal or apparently equally enlarged, suggesting an internal hydrocephalus, then air should always be used. The differential diagnosis between a midline, interhemispheric, supratentorial tumor and a lesion in the posterior fossa cannot be made by ventricular estimation alone. A lesion in either of these positions may cause an internal hydrocephalus. It is only by examina-

9. Dandy, W. E.: Surg., Gynec. & Obst. **36**:641, 1923. Grant, F. C.: ibid. **46**:689, 1928.

tion of the x-ray films, to see whether or not the third ventricle can be clearly visualized, that this differential diagnosis is made (figs. 5*A* and 7*A*). Furthermore, we have in two cases revealed the presence of a tumor within a lateral ventricle by a ventriculogram when ventricular estimation alone would have been misleading, since a marked bilateral internal hydrocephalus was present in both instances. A tap alone without the injection of air would have suggested a lesion of the third ventricle or of the posterior fossa.

In the localization of lesions causing increased intracranial pressure and therefore strongly suggesting a neoplasm, we prefer ventriculography to encephalography. This opinion may well be subject to revision, but such is our belief at present. Although we have repeatedly used encephalography in tumor of the brain, as table 4 shows, we dislike it, especially in lesions of the posterior fossa, because of the danger of precipitating an intracranial crisis by lumbar puncture. Again, bilateral ventricular tap, by the technic described, may give definite evidence of the position of the tumor without the necessity for insufflating any air.

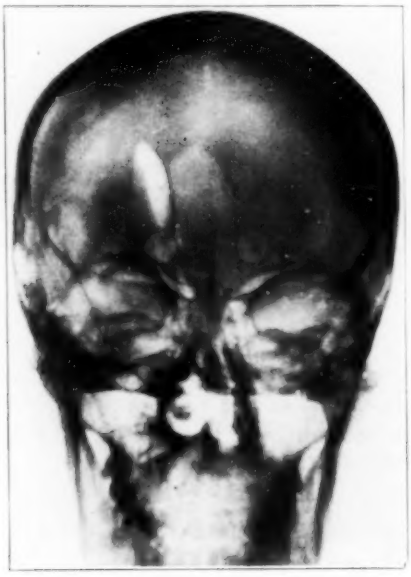

Fig. 1 (case 1).—Ventriculogram of a left frontal tumor. There was no neurologic evidence of the position of the tumor. Localization was determined by the ventriculogram. Note the lateral ventricle deflected to the right by the tumor. Note the symmetrical placing of the trephine openings for tapping of the ventricle. Operation revealed a large cystic glioma, which was partially removed. The patient recovered.

Furthermore, encephalography unquestionably produces a more severe reaction than does ventriculography. If there is one fact that has impressed itself by bitter experience on the neurosurgeon, it is that if a tumor can be located on the films after the injection of air, immediate operation for its removal is essential. Unless prompt surgical measures are adopted, the reaction following the injection of air by either method may be fatal. Following encephalography, we have repeatedly seen patients so severely shocked that immediate operation was out of the question. Later, increasing signs of pressure forced operation under much less favorable circumstances.

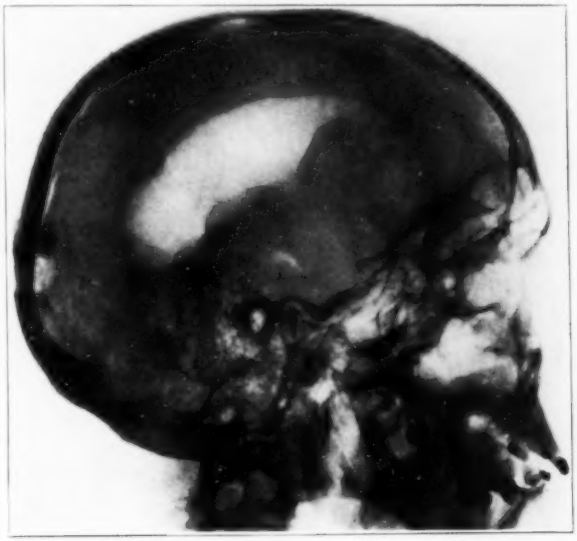

Fig. 2 (case 2).—Large right frontal intraventricular tumor impinging on the right lateral ventricle. The tumor was localized by ventriculogram and removed. This is the type of case with bilateral internal hydrocephalus and a tumor in the cerebral hemisphere in which ventriculography rather than ventricular estimation should be done. Ventricular estimation under these circumstances would have suggested a midline lesion or a lesion of the posterior fossa.

Ventriculography is, of course, a major surgical procedure requiring more technical skill than encephalography, but, even so, it is less distressing to the patient. Furthermore, if following a ventriculogram the localization cannot be made, or if for some good reason operation must be postponed, the air can be removed by a second tap. This reduces the chances of a severe, possibly fatal, reaction. Following encephalography, the air cannot be easily removed, which may be distinctly disadvantageous.

Ventriculography is said to be more dangerous than encephalography and to have a higher mortality. Nevertheless, in comparing the mortality with these two methods, as Jüngling [10] has remarked, the type of case in which each has been used must always be considered. Ventriculography has been employed almost exclusively in tumors of the brain with increased intracranial pressure, frequently as a last resort and under unfavorable conditions. Encephalography, on the other hand, has been used in all manner of cases, without pressure and with the patients usually in good physical condition. Naturally, the resulting mortality has been lower. If ventriculography had been used as promiscuously and widely as encephalography, the subsequent mortality might well be relatively the same. It is interesting to note from a careful review of the literature that of 42 deaths due to encephalography, 20 were in cases of tumor. This is evidence that when used under similar conditions there will not be much difference in the mortality from either method.

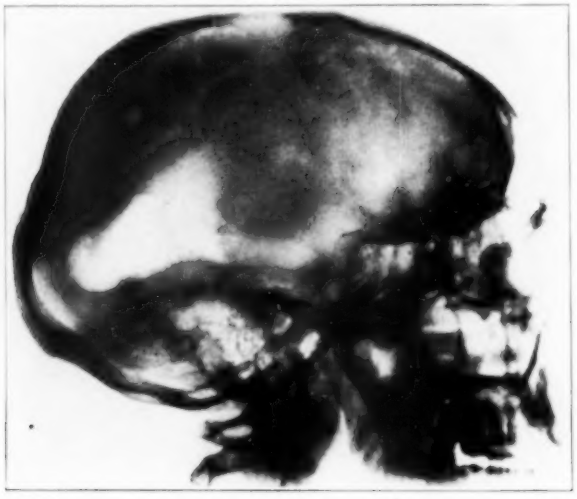

Fig. 3 (case 3).—Tumor in the right parietotemporal region blocking the anterior and inferior horns of the right lateral ventricle. The ventriculogram confirmed the neurologic findings. The tumor was exposed and removed.

Four years ago, I published [11] the results following ventriculography in 392 cases furnished me in great measure through the cooperation of the Society of Neurological Surgeons. The mortality was 8.2 per cent.

10. Jüngling, O.: Klin. Wchnschr. **7**:2350, 1928.

11. Grant, F. C.: Ventriculography: A Review Based on the Analysis of Three Hundred and Ninety-Two Cases, Arch. Neurol. & Psychiat. **14**:513 (Oct.) 1925.

This figure has been widely quoted as evidence of the hazards of this procedure. In the present series of 160 cases from our own clinic, the mortality is 6.2 per cent (table 1). This mortality has been strictly interpreted, 5 of the 10 patients being in desperate condition at the time of the injection of air. Three other patients died from four to nine days after the procedure, a further operation having been refused as the tumor was localized deep in the midbrain. Two patients succumbed from intraventricular hemorrhage, as the exploring cannula punctured the tumor in attempting to reach the ventricle. Consequently, the original mortality figures presented seem to us to be evidence of

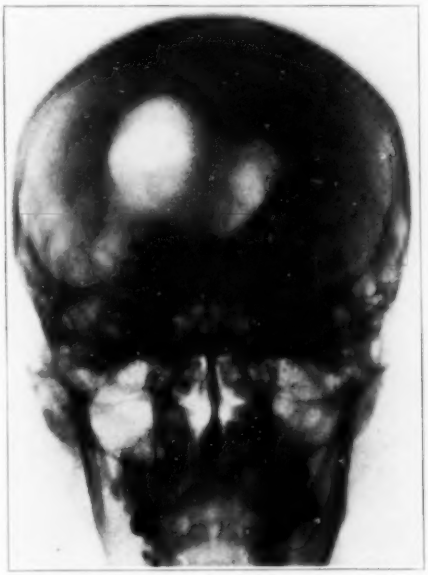

Fig. 4 (case 4).—Tumor of the occipital lobe, blocking the inferior horn of the lateral ventricle. The patient was stuporous at time the ventriculogram was taken. Neurologic examination was impossible. Localization was made by the ventriculogram alone.

the serious situations in which it was used and of our inexperience with the method rather than a correct estimation of present conditions. In support of this opinion, it should be said that in the last 75 cases from this clinic, covering a period of twenty-four months, there has been no mortality attributable to ventriculography.

It is in group VII (table 1) that the real value of ventriculography lies. These patients all had tumors, but there was no neurologic evidence as to the position of the growth. It has been suggested that tumors that can be localized by the injection of air must be large and deep-

seated and, therefore, presumably inoperable. However, 21 of the 48 tumors were successfully extirpated with apparently permanent relief. These particular patients surely were rescued from a speedy death by ventriculography. If it had been necessary to postpone operation until definite focal symptoms developed, the tumor might have reached such a size that complete extirpation would have been impossible, or the constant intracranial pressure have so damaged the optic nerves that

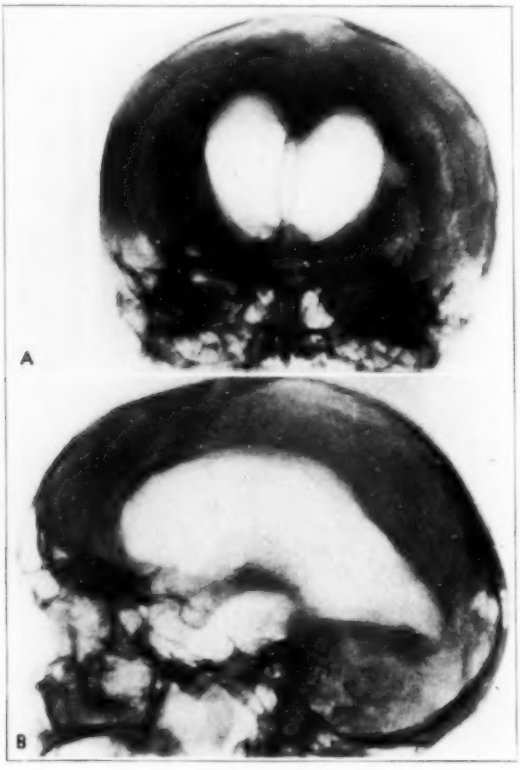

Fig. 5 (case 5).—*A*, anteroposterior ventriculogram in a case of tumor of the anterior part of the third ventricle. Note the marked bilateral internal hydrocephalus with complete absence of the third ventricle. *B*, lateral view in the same case. Note the complete absence of the third ventricle, the aqueduct and the fourth ventricle.

even after a successful operation vision would be much impaired or even lost.

ENCEPHALOGRAPHY

Encephalography has a much wider field of application that ventriculography, owing to the fact that it is a simpler procedure and with

reasonable precautions in technic and in the selection of patients shows a mortality of less than 0.3 per cent (table 3). In our series of 325 cases there has been only 1 death. Nevertheless, it is the ease of performance that may readily constitute one of its major hazards. It is so simple to do that it can be easily abused, and the main contraindication to its use, increased intracranial pressure, can be overlooked. Just as certainly as encephalography is used promiscuously in the presence of high spinal pressure, the mortality will increase. It is by no means only in the presence of increased pressure that the danger from encephalography lies. Elderly, debilitated patients may not react well to the procedure. Guttmann and Kirschbaum [12] have noted the frequency with which a fatal bronchopneumonia may follow the injection of air in such cases. Martin and Uhler [13] and Mader [14] have stated that infants

TABLE 3.—*Summary of Three Hundred and Twenty-Five Cases of Encephalography*

Epilepsy	72
Posttraumatic epilepsy	51
Posttraumatic headache	41
Tumors of the brain	
A. Verified	31
B. Unverified	15
C. Suspected	23
Posttraumatic sequelae (exclusive of epilepsy and headache)	19
Headache (not traumatic)	16
Mental deficiency	14
Chronic encephalitis	13
Multiple sclerosis	12
Cerebral syphilis	5
Cerebral arteriosclerosis	4
Defects from trauma sustained at birth	6
Acute cranial injury	3
Total	325

and young children may suffer severely. My associates and I saw a baby (not under our care) with a mild case of early hydrocephalus succumb promptly to the shock of the procedure. So we cannot accept encephalography as an entirely harmless method of diagnosis, and believe it should not be employed without due consideration of the patient's general condition.

The technic of encephalography has been so frequently described that it needs no further comment. It is our opinion that the simplest methods are the best. We have used the two needle technic advised by Bingel [15] and the insufflation of oxygen or carbon dioxide as suggested by Denk,[16] and have tried out thoroughly the apparatus described

12. Guttmann, L., and Kirschbaum, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:590, 1929.

13. Martin, C. L., and Uhler, C.: Am. J. Roentgenol. **9**:543, 1922.

14. Mader, A.: Med. Klin. **19**:1427, 1923.

15. Bingel, A.: Deutsche Ztschr. f. Nervenh. **72**:358, 1921.

16. Denk, W.: Ztschr. f. ärztl. Fortbild. **20**:426, 1923.

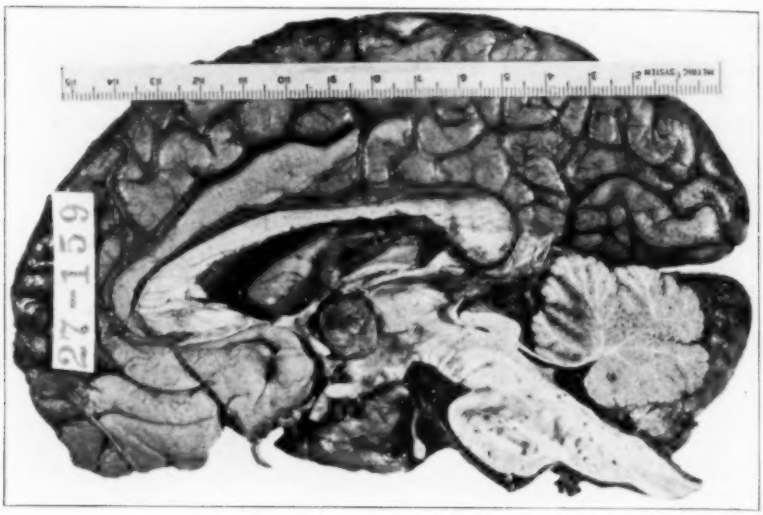

Fig. 6 (case 5).—Section of the brain, showing the position of the tumor in the third ventricle, with marked dilatation of the lateral ventricles and little or no change in size of the third ventricle, the aqueduct or the fourth ventricle.

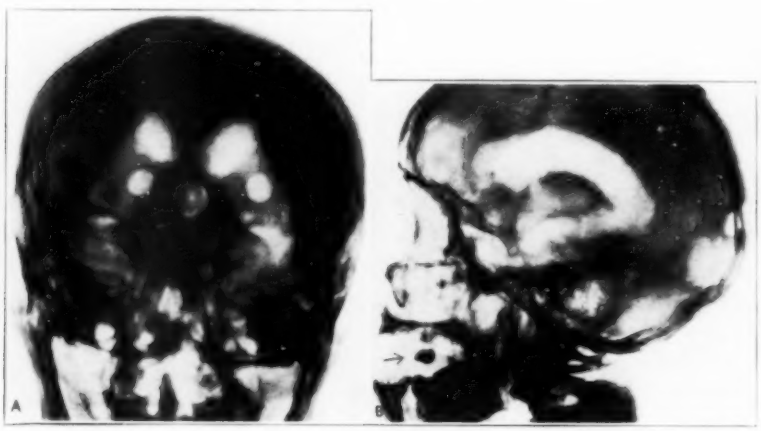

Fig. 7 (case 6).—*A*, anteroposterior ventriculogram, localizing the tumor in the posterior fossa. The tumor was found and removed from the right cerebellar hemisphere. Note the marked dilatation of the lateral and also the third ventricle. Dilatation of the third ventricle is evidence that the tumor lies in the posterior fossa. Compare with figure 5 *A* (case 5). *B*, lateral view of the same case, showing the marked dilatation of the lateral and third ventricles. The upper end of the fourth ventricle can be seen just posterior to the shadow of the mastoid cell.

by Liberson.[17] However, a single needle with a three-way stopcock, one opening for the attachment of a water manometer, one for the escape of the fluid and one for the insufflation of air, by means of a 10 cc. syringe, seems to produce excellent films with a minimum of effort. We never hesitate to aspirate the fluid with the syringe if it will not escape freely. Every effort is made to remove all the fluid by rotating the head and elevating the pressure by obstruction of the jugular veins. Only an equal, or usually a smaller, amount of air is introduced as compared with the fluid removed. We agree with Guttmann[18] that to obtain good films all the fluid must be withdrawn in every case.

The removal of a standard amount of fluid may give unsatisfactory results because the ventricles and subarachnoid spaces differ so markedly in size from patient to patient. Hence, there is no possible way of foretelling in each case the exact amount of fluid that must be drained

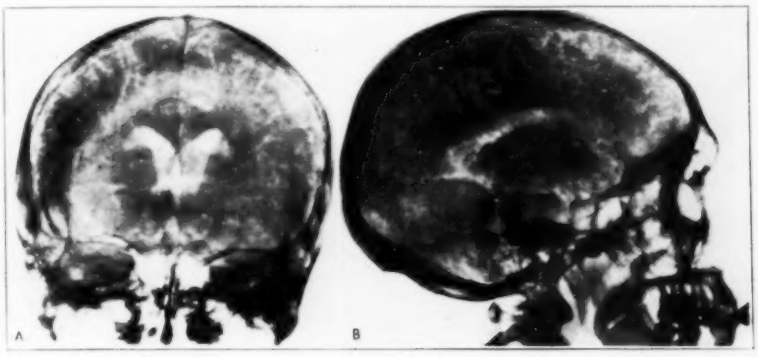

Fig. 8 (case 7).—Normal encephalograms. *A*, anteroposterior view. The patient, a man, aged 28, had atypical facial neuralgia. The pressure of the spinal fluid was 500 mm. of water in the sitting position; 125 cc. of fluid was removed, and 120 cc. of air was injected. Note the typical butterfly picture of the lateral ventricles, with the shadow of the third ventricle lying between them. There is an equally distributed normal amount of air in the subarachnoid channels over both cortices. *B*, lateral view. Note the mild dilatation of the subarachnoid air channels bilaterally with the normal basilar cisternae and the third and fourth ventricles. It should be noted further that the posterior and inferior horns of the lateral ventricles are not well filled.

to obtain an encephalogram that completely outlines the intracranial spaces. While the intracranial pressure should never be allowed to rise above that obtained at the initial puncture, no especial attempt is made to keep it at this level at all times. In earlier cases, an effort was made to minimize the reaction by careful avoidance of marked fluctuations in

17. Liberson, F.: Am. J. Roentgenol. **15**:231, 1926.

18. Guttmann, L.: Psychiat.-neurol. Wchnschr. **30**:432 and 523, 1928.

intracranial presure, but the results did not justify the effort. Wartenberg [19] stated that too rapid injection of air is the cause of the later discomforts, while Trömner [20] expressed the belief that the slow removal of fluid reduces subsequent distress. I do not believe that the prevention of variations in pressure, the speed with which the fluid is withdrawn or the air insufflated or the amount of the exchange between fluid and air has any bearing on the severity of the after-effects.

Roughly, 8 out of 10 patients have considerable distress, no matter how careful the technic may be. The preoperative administration of from 5 to 10 Gm. of amytal by mouth has proved effective in making these patients more comfortable. Following its use, they have a little less discomfort during the procedure and considerably less afterward.

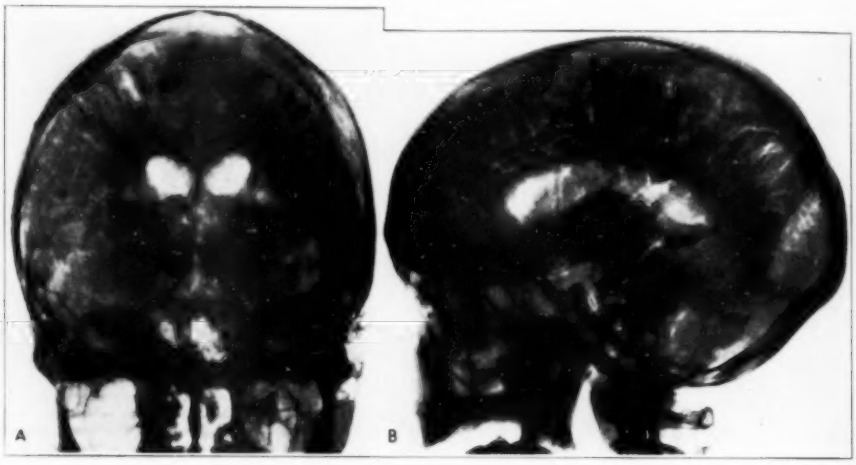

Fig. 9 (case 8).—*A*, atrophy of the subarachnoid spaces. There is a moderate dilatation of the ventricles. The patient, a man, aged 25, had essential epilepsy. The pressure of the spinal fluid was 520 mm. of water in the sitting position; 140 cc. of fluid was removed, and 135 cc. of air was injected. Note the symmetrical dilatation of the lateral ventricles, with bulging in the upper inner edge of the butterfly figure. Compare with figure 8 *A*, in which this line is straight and sharp. *B*, lateral view. Notice the dilated subarachnoid channels. There are some dilatation and rounding of the outline of the lateral ventricle with failure to fill the inferior horn. The basilar cisternae are slightly dilated. The fourth ventricle is well shown. This patient had moderate epilepsy.

At the time the encephalogram is taken, sweating, headache, nausea, vomiting and prostration, with at times a slow pulse, are noted. On 4 occasions convulsions occurred. Herrmann and Herrnheiser [21] have

19. Wartenberg, R.: Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:585, 1925.

20. Trömner, E.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **31**:423, 1923.

21. Herrmann, G., and Herrnheiser, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **96**:730, 1925.

reported this complication. Liebermeister [22] and Bruskin and Fraenkel [23] expressed the belief that the headache is more severe in cases with extensive arachnoid adhesions and is due to the breaking up of these adhesions by the air. We can throw no light on this theory, although it is my impression that we have noted headaches of marked severity in patients who showed apparently normal encephalograms. A rise in temperature of 1 or 2 degrees is common. Every case in which lumbar puncture was done after this procedure showed an increase in cells in the spinal fluid, running as high as 4,500 in 1 instance. The rapidity with which the air is absorbed seems to depend on the amount introduced. In practically normal patients, it will have disappeared in

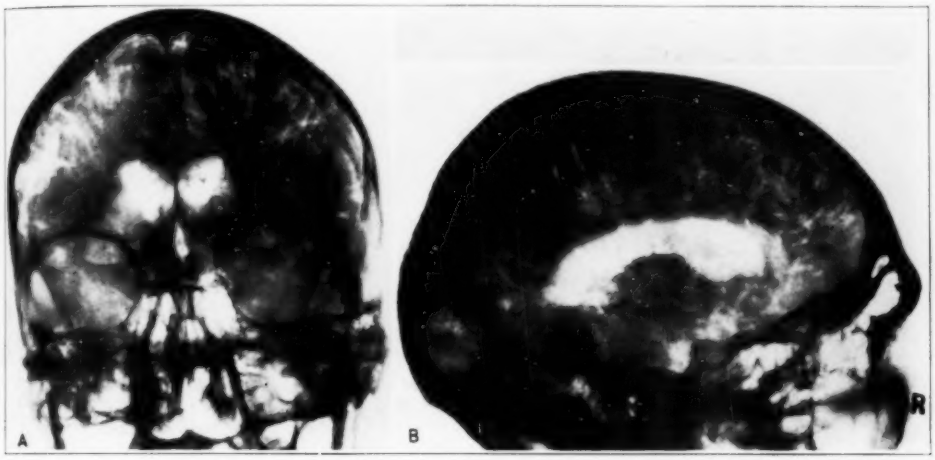

Fig. 10 (case 9).—*A*, marked dilatation of the lateral ventricle and the subarachnoid space. The patient was a man, aged 36, with idiopathic epilepsy of the severe type. He had had three or four convulsions a month for the past twenty years. The initial pressure of the spinal fluid was 500 mm. of water; 160 cc. of fluid was withdrawn, and 155 cc. of air was injected. Anteroposterior view; note the bulging dilatation of the lateral ventricle and the dilated third ventricle. There is atrophy of the cortex, with marked dilatation of the subarachnoid channels. Definite atrophy can be noted in the region of the insula on one side. *B*, lateral view. Note the dilated lateral ventricles, with poorly filled posterior and inferior horns. The third ventricle and the upper end of the aqueduct can be seen. The fourth ventricle is hidden behind the mastoid cell. The basilar cisternae show moderate dilatation.

seventy-two hours, but if the spaces are markedly dilated it may be present much longer. Fluoroscopic studies made in 3 cases, as the fluid

22. Liebermeister, G.: Ergebn. d. inn. Med. u. Kinderh. **25**:901, 1925.

23. Bruskin, J., and Fraenkel, S.: Fortschr. a. d. Geb. d. Röntgenstrahlen **34**: 578, 1926.

was removed and the air introduced, seemed to show that the basilar and subarachnoid channels filled before the ventricles.

The injection of air is always made in the sitting position, and this position is maintained until after the films are made. This technic probably gives better definition of the subarachnoid spaces over the cortex, but certainly, in most instances, results in a failure of the air to fill the posterior and inferior horns of the lateral ventricles. If for any special reason it becomes necessary to fill the postero-inferior horns, the patient can be placed on his face and lateral views obtained as in ventriculography. The routine roentgen exposures are in the

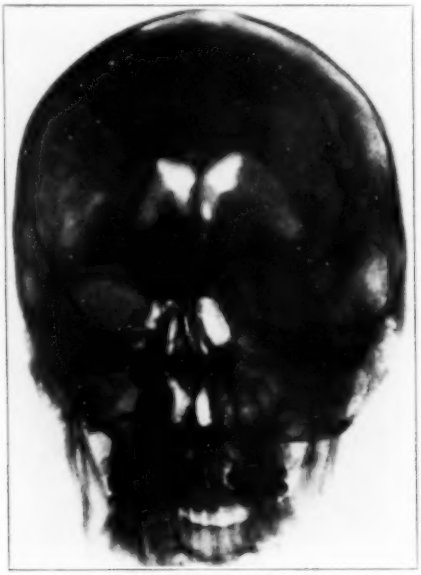

Fig. 11 (case 10).—Unilateral arachnitis with the ventricle on the side of the arachnitis enlarged, in a man, aged 24, with posttraumatic epilepsy of the jacksonian type. The initial pressure of the spinal fluid, in the erect position, was 550 mm. of water; 140 cc. of fluid was removed, and 135 cc. of air was injected. A subsequent operative procedure demonstrated the subarachnoid channels well filled with fluid over the left cerebral cortex. Note the left lateral ventricle pulled out to the left and the lack of air markings over the left cortex.

anteroposterior and postero-anterior planes, with bilateral stereoscopic films. The Bucky diaphragm is always used. The tube is placed at a standard distance of 44 inches (111.76 cm.) from the films. Great care is taken in the frontal and occipital exposures to have the head exactly centered and not rotated, and to be certain that the frontal sinuses lie well below the plane of the third ventricle.

Sixty-nine cases of suspected tumor of the brain or some other expanding lesion are included in the series (table 4). In 31 instances (26 cerebral tumors, 1 chronic subdural hemorrhage, 1 frontal gumma, 1 extradural cerebellar abscess, 1 pontile tumor and 1 case of "arach-

TABLE 4.—*Results of Encephalography in Sixty-Nine Cases of Tumor of the Brain*

Tumors of the brain verified	31
Tumors of the brain unverified	15
Tumors of the brain suspected	23
Total	69
Failure of air to reach ventricles making localization impossible	9
Percentage of failures	19.5

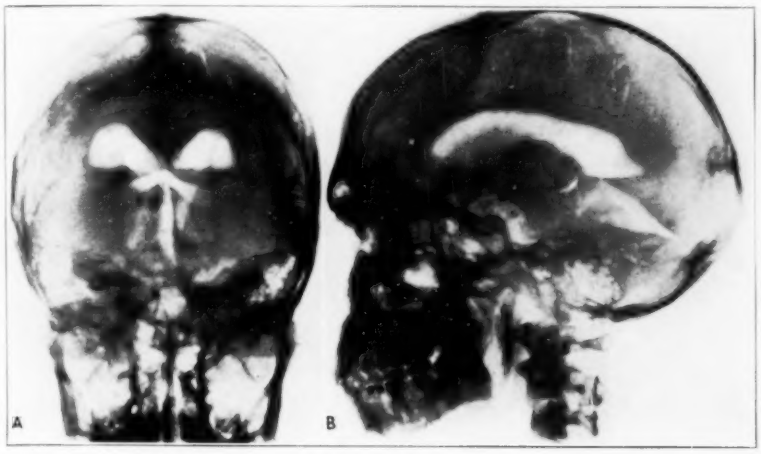

Fig. 12 (case 11).—*A*, bilateral arachnitis, with moderate symmetrical dilatation of the ventricles. There is air in the cisterna vena magna cerebri and in the cisterna interpeduncularis. The patient was a boy, aged 17, who had had moderate essential epilepsy for the past two years, with general convulsions. The pressure of the spinal fluid was 450 mm. of water; 125 cc. of fluid was withdrawn, and 125 cc. of air was injected. *B*, lateral view. Note particularly the absence of subarachnoid air markings with dilated lateral ventricles and a dilated third ventricle. There is a large amount of air in the cisterna vena magna cerebri and the cisterna interpeduncularis. The basilar cisternae are also dilated.

nitis" over the basilar cistern), operation verified the encephalographic interpretations. Although the presence of a tumor seemed unquestioned clinically, in 9 of the remaining 15 cases the amount of air introduced by lumbar puncture proved to be insufficient for diagnosis. In 5 of these 9 cases the tumor was subsequently localized by ventriculography. This is a higher percentage of failure (19.5) in localization of tumors than in ventriculography (10.6).

Furthermore, the 1 fatality in our series of 325 cases occurred in a patient who had an internal hydrocephalus, with 2 diopters of choked disk, a spinal fluid pressure of 300 mm. of water, and encephalographic findings suggesting a tumor in the posterior fossa. Unfortunately, an autopsy was refused in this case. Furthermore, of the 69 cases, only 23 (9 verified and 14 suspected) showed an increased pressure, in no instance over 300 mm. of water in the prone position, and none showed a choked disk of over 2 diopters. It may well be, therefore, that the low mortality reported is due to this conservative attitude in selecting the cases. A prompt inspection of the x-ray films is always made, and if a tumor is found immediate operative intervention is carried out.

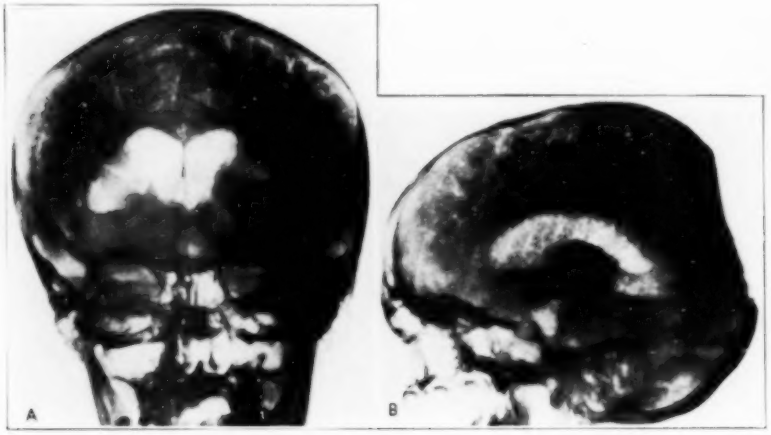

Fig. 13 (case 12).—*A*, bilateral ventricular enlargement, more marked on the right than on the left. There is a bilateral symmetrical dilatation of the subarachnoid spaces. The patient was a man, aged 22, who had been kicked in the back of the head by a mule. He had a compound comminuted fracture, with a subsequent large cranial defect in both occipital regions. He had posttraumatic epilepsy, of the severe type. The initial pressure of the spinal fluid was 600 mm. of water; 180 cc. of fluid was withdrawn, and 170 cc. of air was injected. Note the dilatation of the lateral ventricles, which is more marked on the right than on the left, with symmetrical atrophy of the subarachnoid channels. *B*, lateral view. Note the dilated lateral ventricles and subarachnoid spaces, the cranial defect in the occipital region and, beneath it, an area of arachnitis probably due to local meningeal adhesions.

The chief objection to the use of encephalography in localizing tumors of the brain, aside from the higher percentage of inaccuracies resulting from this method and the necessity of limiting its use to cases that show little or no pressure, is the shocked condition in which this procedure leaves so many patients. An exploration, if indicated by the

localization of a tumor, is out of the question for at least twenty-four hours in most cases. In over half of the 37 patients operated on (31 verified, 6 unverified), the intervention had to be postponed for at least forty-eight hours. After our experience with ventriculography, the necessity for this delay after the injection of air caused much concern. In none of the cases was the initial pressure much above normal. It is probably due to that fact that in only 2 cases did the situation become so serious that an emergency operation was required. Both of these patients died, although in 1 case a small cortical meningioma, easy to extirpate, was encountered.

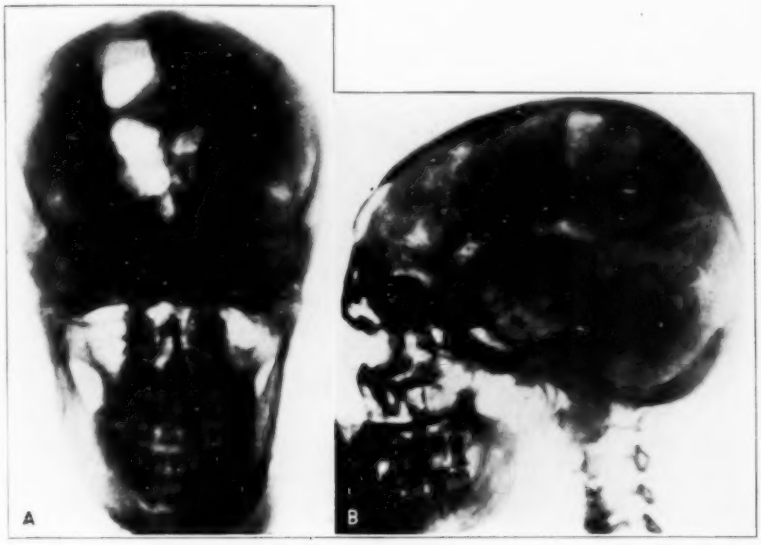

Fig. 14 (case 13).—*A*, posttraumatic porencephalic cyst in a man, aged 32, who had been injured two years previously. He had had jacksonian epilepsy of the moderate type for the last year. Note the dilated lateral ventricle, with a large cyst lying above it. The initial pressure of the spinal fluid was 600 mm. of water; 160 cc. of fluid was withdrawn, and 155 cc. of air was injected. *B*, lateral view. Note the position of the cyst and the dilatation of the subarachnoid channels in front and behind the cystic area. About the cystic area there is arachnitis.

The localization of tumors of the brain by encephalography is based on precisely the same findings as have been described with ventriculography. The common reason in cases of tumor for an inability to make a diagnosis from the films is lack of filling of the lateral ventricles. Spohn,[24] Reale [25] and Koschewnikow and Fraenkel [26] confirmed this

24. Spohn, W.: Psychiat.-neurol. Wchnschr. **27**:504, 1925.

25. Reale, M.: Riforma med. **44**:1047, 1928.

26. Koschewnikow, A., and Fraenkel, S.: Ztschr. f. d. ges. Neurol. u. Psychiat. **103**:593, 1926.

opinion. It should be noted that in only 3 of the 31 verified and 2 of the 15 unverified cases did the tumor lie in the posterior fossa. I do not believe that encephalography should be used if a subtentorial lesion is suspected. Although 5 of the verified tumors lay in the pituitary region, the technic advocated by Heidrich,[27] whereby a lateral plate is taken with the head hanging down, has not been used. Furthermore, the single case of posttraumatic pachymeningitis hemorrhagica interna in this series showed an arachnitis over the cortex covered by the clot, with impingement on the underlying ventricle and not the "sickle-shaped" air bubbles over the cortex described by Reichmann.[28]

The only information of diagnostic value obtainable by using encephalography rather than ventriculography in tumors of the brain is the fact that by the former technic the cortical arachnoid channels

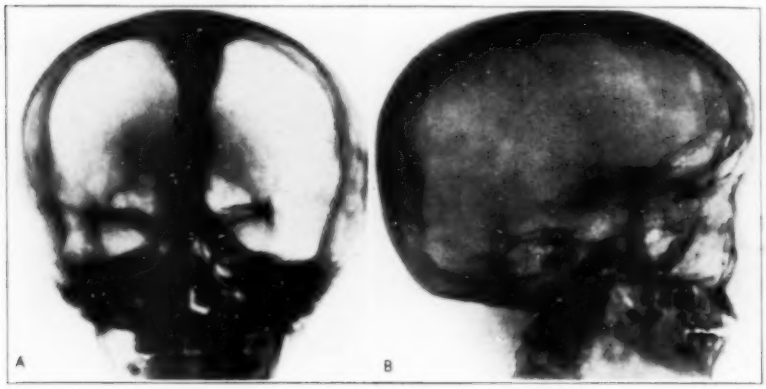

Fig. 15. (case 14).—*A*, anteroposterior view of an enormous congenital hydrocephalus, in a colored child, aged 12 years. The patient was ambulant, with no neurologic symptoms except a very large head and a mental development of a child of 6; 950 cc. of fluid was removed, and 950 cc. of air was injected. Curiously enough, there was no reaction following the taking of the encephalogram. Note the enormous, dilated lateral ventricles without air markings and the entire absence of the third ventricle. *B*, lateral view showing the enormous internal hydrocephalus and the dilated lateral ventricles.

are outlined. This fact may be of some value, for we found that in 6 of 9 cases of noninfiltrating tumor, 8 meningiomas and 1 cholesteatoma, these channels on the side of the tumor were either partially or completely filled with air, while in all the 11 cases of gliomatous tumor the spaces were obliterated. This difference may be of importance from a prognostic point of view, although in any event operation should be performed.

27. Heidrich, L.: Beitr. z. klin. Chir. **142**:837, 1928.
28. Reichmann: Deutsche Ztschr. f. Nervenh. **81**:304, 1924.

The chief value of encephalography to a neurosurgeon lies in its negative results. It is an excellent method by which the necessity for surgical intervention can be eliminated. Once the lesions, such as a tumor, an abscess, a clot, an internal hydrocephalus, a porencephalic cyst or a lateral ventricle dilated and pulled outward to the cortex, indicating a posttraumatic scar, that may require surgical intervention are ruled out, however, encephalography ceases to be of value in differential diagnosis, for there is no encephalographic picture typical of any one organic disease of the brain.

For example, the discovery of generalized cortical atrophy, as shown by enlarged subarachnoid spaces distributed equally over both cerebral hemispheres, with moderate dilatation of the lateral, third and fourth

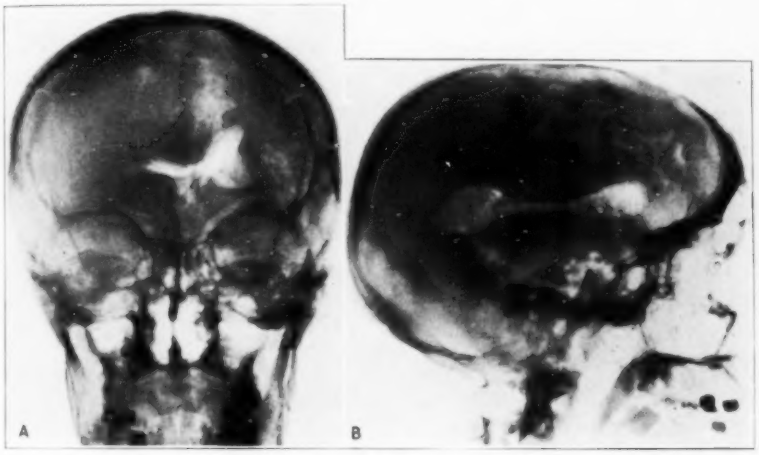

Fig. 16 (case 15).—*A*, encephalogram, anterolateral view, in a case of meningioma of the right hemisphere in a man, aged 32. He had weakness of the left extremities, mild jacksonian epilepsy and no evidence of pressure in the eyegrounds. The initial pressure of the spinal fluid was 500 mm. of water in the erect position; 130 cc. of fluid was removed, and 125 cc. of air was injected. Note the depression of the right lateral ventricle and the slight shift of the ventricular system to the left. *B*, lateral view. Note the depression of the edge of the right lateral ventricle, with dilated arachnoid markings. We have noted dilated arachnoid markings over infiltrating tumors of the meningioma type, while infiltrating gliomatous tumors seem to obliterate the overlying cortical markings. In this instance the differential diagnosis was made between tumor and essential epilepsy by the ventriculogram. The tumor was exposed and removed.

ventricles and basal cisternae, is frequent enough, and one might suspect it to be characteristic of a single organic disease of the brain represented clinically by a definite, well recognized symptom complex. On the contrary, these encephalographic observations have been noted in epilepsy, in posttraumatic headache, in early dementia paralytica, in multiple

sclerosis, in parkinsonism and in patients who showed no demonstrable neurologic signs of any kind. In fact, although the encephalographic picture may be very clear and easy to describe, we agree with Fischer [29] that its final interpretation depends on the accompanying clinical observations; even with the clinical observations one may easily be drawn into error.

In discussing the question of "arachnitis," it was stated that in several cases of jacksonian epilepsy an encephalogram showed complete failure of filling of the subarachnoid air spaces over that cortex which the distribution of the epileptic seizures indicated to be the point of irritation. Widespread cortical adhesions were suspected, but surgical intervention revealed nothing except overfilled edematous subarachnoid spaces, from which the fluid had not been drained in spite of every effort to accomplish its removal. In 3 of these cases, the opposite or air-filled cortex was also later exposed, and certainly to the naked eye, at least, no difference existed in the appearance of the two sides. Presumably, on the undrained side a block of some kind must exist at the base, possibly where the main subarachnoid channels supplying the cortex leave the basilar cisterns. This obstruction cannot be complete, for, if so, one would expect little or no fluid in the cortical spaces; but it must be just sufficiently impermeable to prevent removal of fluid and entrance of air. Does this trapping of the fluid in the subarachnoid spaces have any bearing on the production of epilepsy? Curiously enough, in 3 cases of "arachnitis" over that cortex from which the fits originated, the protein content of the fluid taken from this area was 5 or 6 times higher than in the spinal fluid obtained by puncture. The high protein content of the fluid might conceivably be an irritant initiating the fits. Most cases of jacksonian epilepsy, however, do not show undrained cortical channels. Furthermore, the protein content in the spinal fluid in essential epilepsy is not increased, as might be expected if the convulsions were due to a chemical irritation.

In an attempt to correlate the clinical symptoms and encephalographic details and to determine how much bearing an abnormal amount of subarachnoid fluid has on the production of epilepsy and headache, we have analyzed the findings in 3 groups of cases: epilepsy, posttraumatic epilepsy and posttraumatic headache. In the epilepsy group are included all cases showing epilepsy of any type, with no history of trauma at birth or later, without clinical or serologic evidence of syphilis and with tumors of the brain eliminated by the injection of air. The traumatic epilepsy group is made up of nonsyphilitic patients in whom the fits definitely appeared as a result of trauma. In the posttraumatic

29. Fischer, M.: Arch. f. Psychiat. **79**:96, 1926.

headache series, the headache appeared subsequent to cranial injury and was attributed thereto by the patient.

In classifying these groups from the encephalographic standpoint, it has been attempted to decide whether or not the findings were normal (not an easy thing to do in view of our slight knowledge of precisely what constitutes a normal encephalogram) or whether the films showed moderate or marked atrophy or moderate or marked arachnitis symmetrically or asymmetrically in the subarachnoid channels, with or without enlargement or distortion of the lateral ventricles. This is admittedly a rough classification, but any attempt to go into greater details presents many difficulties, for individual variations are numerous.

Of the 72 cases of epilepsy, 16 gave what we considered to be normal encephalographic pictures; 40 showed various degrees of atrophy, and

TABLE 5.—*Encephalographic Findings in Seventy-Two Cases of Epilepsy*

I. Normal encephalograms		16	22.2%
II. Atrophy principal finding		40	55.6%
A. Symmetrical	35		
1. Ventricles dilated, subarachnoid channels normal	2		
2. Ventricles normal, subarachnoid channels dilated	21		
3. Ventricles dilated, subarachnoid channels dilated	12		
B. Asymmetric	5		
1. Ventricles normal, subarachnoid channels on one side dilated	3		
2. One ventricle dilated, subarachnoid channels normal	2		
III. Arachnitis principal finding		16	22.2%
A. Symmetrical	10		
1. Ventricles dilated, in subarachnoid space bilateral arachnitis	10		
B. Asymmetric	6		
1. Ventricles normal, in subarachnoid space unilateral arachnitis	5		
2. One ventricle dilated on the side of arachnitis in the subarachnoid space	1		
IV. Ventricular asymmetry		4	5.5%

16 arachnitis. Of the 40 cases, 35 showed moderate symmetrical dilatation of all the spaces; 5 a dilatation that was asymmetric, one ventricle being larger than the other. Of these 35 cases, in 2 the ventricles alone were enlarged, the subarachnoid channels being normal; in 21 the ventricles were normal, but the subarachnoid channels were moderately dilated, while in 12 both ventricles and subarachnoid spaces were increased in size. Sixteen showed arachnitis, in 10 symmetrically over both cortices with moderate enlargement of the ventricles; in 6 the arachnitis was much more marked on one side than on the other. Of the last 6, only in 1 was the ventricle pulled out toward the arachnitis, the wandering ventricle of Foerster [30] and Schwab [31] (table 5).

In the 51 cases in the posttraumatic epilepsy group, 5 showed normal encephalograms, 28 varying degrees of atrophy, and 18 arachnitis. Sixteen of the 28 exhibited different amounts of symmetrical atrophy.

30. Foerster, O.: Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:512, 1925.

31. Schwab, Otto: Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:708, 1925.

Among these 16 the subarachnoid spaces were normal in 4, but the ventricles symmetrically were slightly dilated; in 8 the ventricles were normal, but the subarachnoid channels over both cortices were slightly enlarged, and in 4 both ventricles and cortical spaces were definitely widened. Twelve of the 28 cases presented asymmetric atrophy, one ventricle being larger than the other in 7, although the cortical atrophy was equal on the two sides. Two of these 7 were cases of porencephalic cysts, while in 5 patients one ventricle and the corresponding cortical spaces were enlarged as compared to the dilatation existing on the opposite side. Among the 18 cases of arachnitis, both cerebral cortices were uniformly affected in 7 cases with slight equal ventricular dilatation. In 5, all cortical channels were undrained and one lateral ventricle was larger than the other. In 6, the subarachnoid space on

TABLE 6.—*Encephalographic Findings in Fifty-One Cases of Posttraumatic Epilepsy*

I. Normal encephalograms		5	9.8%
II. Atrophy principal finding		28	54.9%
A. Symmetrical	16		
1. Ventricles dilated, subarachnoid channels normal	4		
2. Ventricles normal, subarachnoid channels dilated	8		
3. Ventricles dilated, subarachnoid channels dilated	4		
B. Asymmetric	12		
1. One ventricle dilated on the side of dilatation in the subarachnoid space	5		
2. One ventricle dilated, subarachnoid space dilated	7		
III. Arachnitis principal finding		18	35.3%
A. Symmetrical	7		
1. Ventricles dilated, in subarachnoid space bilateral arachnitis	7		
B. Asymmetric	11		
1. Ventricles normal, in subarachnoid space unilateral arachnitis	6		
2. In subarachnoid space bilateral arachnitis, one ventricle dilated	5		
IV. Ventricular asymmetry		23	45.0%

one side only failed to fill, and the lateral ventricle on this side was larger. These last 2 pictures represent the true "wandering" ventricle, emphasized as a characteristic posttraumatic observation. This feature has been noted in our series, at least with sufficient frequency to be considered characteristic of this condition; but, as our statistics show, it may also occur in epileptic patients who give no history of trauma. In the 23 cases of posttraumatic epilepsy in which one ventricle was shown by the encephalogram to be larger than the other, a history of injury, particularly to one side of the head, was obtained in 18. In 16 of these cases the side of the trauma and the enlargement of the ventricle corresponded. In 2 patients the distended ventricle was on the opposite side of the head to that on which the injury was received. However, the possibility of damage to the brain by contrecoup probably accounts for this contralateral distortion (table 6).

Among the 41 patients suffering from posttraumatic headache, the encephalograms were considered normal in 6. In 32 cases atrophy was

present, and in only 3 an arachnitis. Of the 32 cases of atrophy, in 21 the cortical air markings were uniformly slightly enlarged on both sides, while the ventricles were normal. In 5 cases both ventricles and cortical subarachnoid spaces were symmetrically enlarged, and in 6 one ventricle was larger than the other, although the subarachnoid spaces were widened on both sides. The 3 cases of arachnitis showed symmetrical cortical involvement, with slight equal ventricular dilatation (table 7).

Comparing the two types of epilepsy, these figures show that in the patients in whom trauma was not a factor in the causation of the fits, the encephalograms were normal in 22.2 per cent, atrophy to a greater or lesser degree was present in 55.6 per cent, and arachnitis to some extent was noted in 22.2 per cent. Ventricular asymmetry was recorded in 4 cases, or 5.5 per cent. The corresponding figures in the post-

TABLE 7.—*Encephalographic Findings in Forty-One Cases of Posttraumatic Headache*

I. Normal encephalograms		6	14.6%
II. Atrophy principal finding		32	78.0%
A. Symmetrical			
1. Subarachnoid spaces dilated, ventricles normal	21		
2. Subarachnoid spaces and ventricles dilated	5		
B. Asymmetric			
1. One ventricle dilated, subarachnoid spaces dilated	6		
III. Arachnitis principal finding		3	7.4%
A. Symmetrical			
1. In subarachnoid spaces bilateral arachnitis, ventricles slightly enlarged	3		
IV. Ventricular asymmetry			14.6%

traumatic group are: normal, 9.8 per cent; atrophy, 54.9 per cent; arachnitis, 35.3 per cent, and ventricular asymmetry, 23 cases, or 45 per cent. The epilepsy following trauma, then, seems to present a definite abnormality in the encephalographic shadows in 95 per cent of cases, while epilepsy in which trauma is not a factor gives almost 25 per cent of normal films. Another striking difference between these groups lies in the fact that following trauma 45 per cent of the cases show ventricular asymmetry, almost 9 times as high a percentage as in the other class. If the 3 nontraumatic epileptic subgroups are considered—the cases presenting apparently normal encephalographic findings plus those in which the subarachnoid spaces showed bilateral atrophy with normal or only slightly enlarged ventricles—it will be found that 70 per cent of our cases show one or the other of these air pictures. This seems to show some connection between excess fluid in the subarachnoid spaces and epilepsy, although it is impossible to determine precisely whether the fluid is the cause of the epilepsy or the epilepsy of the fluid.

In order to try to arrive at a conclusion on this important point, these epileptic and posttraumatic epileptic groups were analyzed from the point of view of attempting to correlate the encephalographic evidences with the severity of the epileptic attacks. Epileptic fits vary so greatly from one patient to another, or even in the same patient, that any classification must be artificial. As we thought that possibly the increased intracranial pressure produced by a major epileptic seizure might force fluid into the subarachnoid channels and ventricles and by constant repetition produce distention and atrophy, these cases were again divided arbitrarily into 3 groups depending entirely on the frequency with which the major fits occurred. Since petit mal seizures apparently do not raise the intracranial tension, they were disregarded

TABLE 8.—*Statistics on Convulsions in Epileptic and Posttraumatic Epileptic Cases*

I. Normal encephalograms		21
5 Mild	23.8%	
9 Moderate	42.8%	
7 Severe	33.4%	
II. Subarachnoid channels dilated, ventricles normal		28
16 Mild	57.0%	
4 Moderate	14.3%	
8 Severe	28.7%	
III. Subarachnoid channels dilated, ventricles dilated		17
5 Mild	29.4%	
4 Moderate	23.5%	
8 Severe	47.1%	
IV. In subarachnoid channels arachnitis, ventricles normal		11
2 Mild	18.2%	
2 Moderate	18.2%	
7 Severe	63.6%	
V. Subarachnoid channels unequally dilated, one ventricle larger than the other		8
2 Mild	25.0%	
1 Moderate	12.5%	
5 Severe	62.5%	

as a basis for classification. The cases with less than 10 major convulsions prior to encephalography are grouped as mild; with from 10 to 20 as moderate, and with over 20 as severe. In the 21 cases with normal encephalograms, 7 showed severe convulsions, 9 moderate and 5 mild. In the 28 cases with dilated arachnoid channels but normal ventricles, 8 showed severe convulsions, 4 moderate and 16 mild. Of the 17 patients with bilateral cortical atrophy plus ventricular enlargement, 8 suffered from severe, 4 from moderate and 5 from mild epilepsy. So it is apparent that there is no definite relationship between the degree of arachnoid and ventricular distention and the severity of the convulsions. There are only two varieties of encephalographic picture that seem to be constantly noted in severe epilepsy: (1) bilateral arachnitis with normal ventricles, in which 7 of 11 cases showed severe fits, and (2) bilateral atrophy, more marked on one side than on the other, with unequal dilatation of the lateral ventricles; 5 of 8 cases each showed over 20 grand mal attacks (table 8).

It may be argued that these apparently inconsistent results are due to faulty technic resulting in incomplete drainage and consequently misleading encephalograms. But in reviewing the notes on these cases, made at the time when the procedure was carried out, in all instances it is stated that every effort was made to remove the fluid completely by rotation of the head, coughing, straining, jugular compression and aspiration by a syringe. So we are convinced that as far as the encephalograms are concerned they illustrate as well as this method permits the degree of dilatation of the arachnoid spaces and the ventricular system. Furthermore, since these encephalograms were all made according to the same technic and the films taken according to a definite standard method, it is not unfair to compare them one with another.

As a result of this review of our series of encephalograms, we frankly are not impressed with the value of this procedure from a diagnostic or prognostic standpoint, except when an expanding mass lesion, as a tumor, abscess or hemorrhage, is present. To be sure, from the films a posttraumatic cortical scar pulling over one lateral ventricle and possibly producing enough irritation to cause epilepsy may be distinguished, but we agree with Fischer [29] and Lennox and Cobb [32] that but little regarding the etiology of genuine epilepsy is shown. We have seen nothing in the cortical air markings to confirm Schuster's [33] suggestion that by this means the presence of an epileptic center can be identified. As our records demonstrate, genuine epilepsy can be accompanied by a great variety of changes in the ventricles and subarachnoid spaces. With regard to the findings in posttraumatic epilepsy, we can only confirm Reichardt's [34] and Wartenberg's [35] opinion that it is impossible to be certain that some of the changes seen on the films and attributed to the injury were not present prior thereto. The often cited case of Koschewnikow,[36] who, in order to obtain a "normal" encephalogram, had an injection of air made on himself, only to find that the subarachnoid spaces over the cortex failed to fill, bear out this idea. If he had had a head injury, this area of "arachnitis" could easily have been attributed to it.

Our series shows a much higher percentage of normal findings in epilepsy than other observers have reported. Tyczka,[37] in 43 patients with jacksonian epilepsy, described only 3 as normal. Weber [38] was

32. Lennox, W. G., and Cobb, Stanley: Epilepsy, Baltimore, Williams & Wilkins Company, 1928.

33. Schuster, Julius: Arch. f. Psychiat. **79**:276, 1926.

34. Reichardt, M.: Deutsche med. Wchnschr. **54**:302, 1928.

35. Wartenberg, R.: Arch. f. Psychiat. **77**:507, 1926.

36. Koschewnikow, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **104**:374, 1926.

37. Tyczka, W.: Neurol. polska **8**:279, 1925.

38. Weber, G.: Fortschr. a. d. geb. d. Röntgenstrahlen **40**:437, 1929.

of the opinion that many of the subarachnoid accumulations of air are accidental, and supported this contention by autopsy results. We believe with Quensel,[39] Hauptmann [40] and Barth [41] that Schwab's [42] and Heidrich's [43] claim that by the use of encephalography cases of traumatic neurosis may be distinguished from true injuries of the brain is not altogether substantiated. The encephalographic changes unfortunately do not seem to run parallel to the severity of the injury, apparently minor blows at times resulting in marked irregularities in air shadows, and vice versa. Again one wonders in these slight injuries with astonishing encephalographic changes just what the condition of the fluid spaces was before the injury occurred.

The posttraumatic headache group gave more uniform results (table 7). A mild degree of atrophy in both the subarachnoid channels and the ventricles appeared so frequently that it might be surmised with

TABLE 9.—*Therapeutic Results in Seventy-Two Cases of Epilepsy*

Followed for 24 months or more			24
Completely relieved (4 taking phenobarbital)	6	25.0%	
Improved	6	25.0%	
Unimproved	12	50.0%	
Followed for from 12 to 24 months			13
80% improved	2	15.3%	
Unimproved	11	84.7%	
Followed for less than 12 months			24
Completely relieved (2 taking phenobarbital)	3	12.5%	
Improved	6	25.0%	
Unimproved	15	62.5%	
Lost			11
Total			72

some assurance that overdistention of the fluid spaces was the cause of the headache. This is contrary to the opinion of Penfield [44] that adhesions cause the pain. We found no definite evidence that adhesions either local or general were commonly present.

Many claims have been made for the therapeutic value of encephalography. We have reviewed the follow-up reports in the 72 cases of epilepsy, 51 of posttraumatic epilepsy and 41 of posttraumatic headache. Tables 9, 10 and 11 show the results in each of these groups. We were rather surprised to note the number of cases of epilepsy and posttraumatic headache in which the patients were relieved of symptoms. However, it must be noted that of the 21 cases in both groups of

39. Quensel, F.: Monatschr. f. Unfallh. **35**:128, 1928.
40. Hauptmann: Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:846, 1927.
41. Barth, A.: Veröffentl. a. d. Geb. d. Med.-Verwalt. **30**:1, 1929.
42. Schwab, Otto: Deutsche Ztschr. f. Nervenh. **89**:44, 1926.
43. Heidrich, L.: Arch. f. klin. Chir. **142**:772, 1926.
44. Penfield, W.: Surg., Gynec. & Obst. **45**:747, 1927.

epileptic patients who were free from fits following encephalography, at least up to the time of our check-up, 12 were taking phenobarbital. As only 3 of these 12 had had phenobarbital before, in the remaining 9 this drug may have had as much to do with the improvement as the injection of air. While we do not recommend encephalography in the treatment for epilepsy, the figures seem to show that in a small percentage of cases the results may be unexpectedly favorable. The litera-

TABLE 10.—*Therapeutic Results in Fifty-One Cases of Posttraumatic Epilepsy*

Followed for 24 months or more			13
Completely relieved	3	24.0%	
Improved	5	38.0%	
Unimproved	5	38.0%	
Followed for from 12 to 24 months			15
Completely relieved	5	33.3%	
(3 taking phenobarbital)			
Improved	3	20.0%	
Unimproved	7	47.7%	
Followed for less than 12 months			11
Completely relieved	4	36.3%	
(3 taking phenobarbital)			
Improved	2	18.1%	
Unimproved	5	45.6%	
Lost			12
Total			51

TABLE 11.—*Therapeutic Results in Forty-One Cases of Posttraumatic Headache*

Followed for 24 months or more			11
Completely relieved	5	45.4%	
Improved	4	36.3%	
Unimproved	2	18.3%	
Followed for from 12 to 24 months			12
Completely relieved	6	50.0%	
Improved	4	33.3%	
Unimproved	2	16.7%	
Followed for less than 12 months			9
Completely relieved	3	33.3%	
Improved	3	33.3%	
Unimproved	3	33.3%	
Lost			9
Total			41

ture on encephalography suggests that although encouraging results in epileptic subjects have at times been obtained (Brehme,[45] Weigeldt,[46] Bingel,[47] Gravenhoff,[48] Schuster,[49] Friedemann,[50] Kissoczy and Wold-

45. Brehme, T.: Abhandl. a. d. Kinderh. u. Grenzgeb. **11**:1, 1926; Encephalography in Children, Berlin, S. Karger, 1926, pp. 6 and 11.

46. Weigeldt, W.: München. med. Wchnschr. **69**:1764, 1922.

47. Bingel, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:323, 1928.

48. Gravenhoff, W.: Med. Welt **1**:249 and 288, 1928.

49. Schuster, Julius: Arch. f. Psychiat. **78**:214, 1926.

50. Friedemann, A.: Deutsche Ztschr. f. Nervenh. **106**:82, 1928.

rich,[51] Tschugunow, Budinoff and Rosanoff,[52] Tyczka,[53] Frisch[54] and Koschewnikow and Fraenkel[55]) relief is not lasting. If cessation of convulsions for two or three weeks is considered a therapeutic triumph, as Emdin[56] claimed, then encephalography is effective. But experience with epileptic patients soon convinces the observer that any new treatment may break up the epileptic cycle for a time at least, and in the majority of cases this seems all that can be expected from an encephalogram. However, it is some satisfaction to the physician to know that after one has put an epileptic patient through the discomforts of an injection of air, showed him the plates and told him that he has a diffuse lesion that cannot be benefited by surgical intervention, the poor fellow has some slight chance in favor of his improvement. Furthermore, when, based on encephalographic studies, treatment with phenobarbital, dehydration or a ketogenic diet is instituted, it must always be remembered that any cessation in convulsions that occurs may be due to encephalography as well as to other types of therapy.

The results of encephalography in the treatment for posttraumatic headache were much more satisfactory than those for epilepsy. However, based on the reports of Penfield,[44] Foerster,[30] Schwab,[42] Wartenberg,[35] Carpenter[57] and Boyd,[58] the high percentage of complete relief or improvement obtained was not unexpected. Penfield, who first pointed out the definite beneficial effect of the injection of air in this condition, stated that headache and dizziness are the chief symptoms. The headache is usually localized near the site of the blow, is commonly dull and hammering and often is made worse on movement or straining. The pain is frequently worse in the morning on first arising. Among the 14 cases in this series in which the patients were completely relieved, the symptoms closely paralleled those he described in 9. In the other 5 cases, the headaches were general, not localized and almost constantly present. We were only able to confirm Penfield's observation of localized cystic collections over the cortex in 5 cases, in 2 of which the patients were improved. But we feel that encephalography is of definite therapeutic value in this distressing posttraumatic condition and should

51. Kissoczy, S., and Woldrich, A.: Med. Klin. **23**:1608, 1927.

52. Tschugunoff, S.; Budinoff, D., and Rosanoff, M.: Fortschr. a. d. Geb. d. Röntgenstrahlen **33**:601, 1925.

53. Tyczka, W.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **44**:489, 1926-1927; footnote 37.

54. Frisch, Felix: Wien. klin. Wchnschr. **43**:615, 1930.

55. Koschewnikow, A., and Fraenkel, S.: Fortschr. a. d. Geb. d. Röntgenstrahlen **36**:1180, 1927.

56. Emdin, P.: Abstr., Zentralbl. f. d. ges. Radiol. **6**:701, 1928-1929; Zentralbl. f. d. ges. Neurol. u. Psychiat. **52**:347, 1929.

57. Carpenter, E.: Southwestern Med. **10**:61, 1926.

58. Boyd, D.: Post-Traumatic Headache Treated by Spinal Insufflation of Air, Arch. Surg. **18**:1626 (April) 1929.

be employed more frequently. Certainly, the injection of air can do little harm, for none of our patients were made worse by its use.

The other groups of cases in this series are too small in number for any definite conclusion to be reached through their review. No certain therapeutic result can be claimed in the treatment of encephalitis, cerebrospinal syphilis or multiple sclerosis. We have had no experience with encephalography in meningitis, although Bingel,[59] Liebermeister,[60] Holtz,[61] Siegl and Sollgruber,[62] Heymann [63] and Hamburger [64] reported some success. Guttmann and Kirschbaum [12] and Ebaugh [65] stated that in tabes and progressive paralysis a prognosis and an evaluation of the results of malarial treatment can be reached from the encephalographic films.

Based on the experience gained from a limited number of children with spastic paraplegia and retarded mentality, due apparently to trauma sustained at birth, we agree with Guttmann [66] and Crothers, Vogt and Eley [67] that by an encephalogram a reasonably accurate prognosis may be obtained as to what the future of the child may be, whether intensive efforts in training are justified and whether surgical intervention is indicated.

CONCLUSIONS

As a result of this review several conclusions have been reached. Unquestionably, the injection of air is of much value both in diagnosis and in prognosis in intracranial disease; in certain conditions the therapeutic results justify its use. We are convinced that in patients with increased intracranial pressure suspected of having a tumor of the brain the air should be introduced by direct bilateral ventricular tap and not by lumbar puncture. Ventriculography gives more accurate information as to the position of a mass lesion with less distress and greater safety to the patient than does encephalography. But in patients without increased tension, for a differential diagnosis between atrophy, sclerosis and tumor, or between traumatic neurosis and true posttraumatic encephalopathy, for prognosis in epilepsy, birth trauma or degenerative disease, or for therapy in posttraumatic headache, an outline of the lateral ventricles and subarachnoid channels should always be obtained by encephalography.

59. Bingel, quoted by Schoenborn, S.: Deutsche med. Wchnschr. **48**:1432, 1922.
60. Liebermeister, G.: Klin. Wchnschr. **4**:73, 1925.
61. Holtz, K.: München. med. Wchnschr. **75**:1274, 1928.
62. Siegl, J., and Sollgruber, K.: Arch. f. Kinderh. **79**:1, 1926.
63. Heymann, P.: Deutsche med. Wchnschr. **51**:1025, 1925.
64. Hamburger, F.: Wien. klin. Wchnschr. **39**:497, 1926.
65. Ebaugh, F. G.; Dixon, H. H.; Kiene, H. E., and Allen, K. D. A.: Am. J. Psychiat. **10**:737, 1931.
66. Guttmann, L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:965, 1929.
67. Crothers, Bronson; Vogt, E. C., and Eley, R. C.: Encephalography in Cases with Fixed Lesions of the Brain, Am. J. Dis. Child. **40**:227 (Aug.) 1930.

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

IV. REACTION OF THE CLASSIC NEUROGLIA

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

The cerebral states following acute injuries to the brain, particularly those included under the elusive term of concussion, have long been the subject of considerable conjecture. A satisfactory physiologic and pathologic explanation for the acute or chronic clinical symptoms manifested has not been clearly established. For example, the individual nervous and mental phenomena that so frequently appear as an aftermath to brain injury have been attributed by some to generalized gliosis or to other diffuse tissue change. To the contrary, there are others who believe that such manifestations are to be explained largely on a functional basis. Is the solution of the problem to be sought in histologic studies? Can sufficient alterations be found in the various cellular elements to account for immediate as well as remote symptoms? What alterations take place in these cells, and what is their significance? In what measure can the reaction of the classic neuroglia be taken as an index of disordered nerve function? These and many other questions arise and demand an answer. As far as we are able to determine, a thorough study of the finer changes in the constituent elements of the nervous system has not been made in cases of injury of the human brain. In this contribution, the fourth of a series of studies,[1] we are concerned with the reaction of the classic neuroglia.

REVIEW OF THE LITERATURE

It is not our purpose to discuss in detail the history of the supporting elements of the central nervous system, as this has been so ably accomplished by others. Since Virchow[2] established the identity of

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From the Neurological Service and the Neuropathological Laboratory of the Los Angeles County General Hospital.

1. Rand, C. W.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: I. Preliminary Report, Arch. Surg. **22**:738 (May) 1931. Rand, C. W., and Courville, C. B.: II. Changes in the Choroid Plexus and Ependyma, ibid. **23**:357 (Sept.) 1931; III. Reaction of Microglia and Oligodendroglia, Arch. Neurol. & Psychiat. **27**:605 (March) 1932.

2. Virchow, R.: Ueber das granulierte Ansehen der Wandungen der Gehirnventrikel, Allg. Ztschr. f. Psychiat. **3**:242, 1846.

cells which constitute the supporting framework of the functional elements, certain definite lines of investigation have been followed. Their histologic character was shown by Golgi,[3] who first demonstrated cellular detail with his silver impregnations, by Weigert,[4] whose staining method demonstrated glia fibrillae, and finally by Cajal,[5] whose gold sublimate method established their absolute identity. The question of a syncytium, first illustrated but not described by Frommann,[6] elaborated more fully by Held[7] and Hardesty,[8] and finally discounted as an artefact of staining by Achucarro,[9] is now of little moment. From the standpoint of classification, the "mossy" and "spider" cells of Golgi were soon described as protoplasmic and fiber cells by Kölliker[10] and Andriezen.[11] In addition to the classic neuroglia, it was soon recognized that some of the interstitial elements could not be demonstrated by any of the existing methods. These have since been recognized as mesodermal (microglia) as well as ectodermal (oligodendroglia) in origin. To these basic studies have been added innumerable other contributions on staining methods, on minute details of their structure, and particularly on their alteration in various pathologic lesions of the central nervous system. Of the latter we have chosen to review only those dealing with the changes in the classic neuroglia following traumatic lesions.

LITERATURE ON NEUROGLIAL CHANGE FOLLOWING EXPERIMENTAL INJURY

In reviewing the literature dealing with neuroglial changes consequent to injury, the following aspects of experimental injury have been

3. Golgi, C.: Sulla fina anatomia della sistemo nervoso, Milan, U. Hoepli, 1886.

4. Weigert, C.: Beiträge zur Kenntnis der normalen menschlichen Neuroglia, Frankfurt, August Weisbrod, 1895.

5. Ramón y Cajal, S.: Sobre un nuevo proceder de impregnacion de la neuroglia y sus resultados en los centros nerviosos del hombre y animales, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:219, 1913.

6. Frommann, C.: Untersuchungen über die normale und pathologische Histologie des centralen Nervensystems, Vienna, Friedrich Frommann, 1876.

7. Held, H.: Ueber den Bau der Neuroglia und über die Wand der Lymphgefässe in Haut und Schleimhaut, Abhandl. d. math.-phys. Kl. d. k. sächs. Gesellsch. d. Wissensch. **28**:199, 1904.

8. Hardesty, Irving: On the Development and Nature of the Neuroglia, Am. J. Anat. **3**:229, 1904.

9. Achucarro, N.: Notas sobre la estructura y functiones de la neuroglia y en particular de la neuroglia de la corteza cerebral humana, Trab. d. lab. de invest. de biol. Univ. de Madrid **11**:186, 1913.

10. Kölliker, A. v.: Handbuch der Gewebelehre des Menschen, ed. 2, Leipzig, W. Engelmann, 1893.

11. Andriezen, W.: The Neuroglia Elements in the Human Brain, Brit. M. J. **2**:227, 1893.

considered: (1) simple puncture wounds, with or without removal of central core, (2) simple linear incisions, (3) extensive brain wounds, (4) embedded foreign bodies and (5) traumatic brain hemorrhage.

Simple Puncture Wounds.—Coen [12] and Tschistowitsch [13] were evidently the first to study experimental puncture wounds of the brain. The latter studied wounds made in the brain of pigeons and dogs with platinum needles, and the cellular reaction which followed from three to one hundred days after injury was noted. He concluded that the connective tissue elements from the pia mater and blood vessels played the chief rôle in the resulting scar. The neuroglia, in his opinion, had to do only with the formation of a narrow zone of sclerosis and the consequent shrinkage of the scar.

Very little experimental work was done after the investigations of Tschistowitsch until Penfield [14] and Penfield and Buckley [15] studied neuroglial changes following both blunt needle and trocar punctures. Where the damaged brain tissue was left in situ, there was a hypertrophy of the regional astrocytes, and the protoplasmic forms were transformed into the fibrous type. The cells assumed a concentric arrangement about the needle tract, with their larger expansions radiating from it, owing to the contraction of the connective tissue core. When the central core was removed by a hollow trocar, there was a minimal amount of connective tissue formation, with only a minor degree of glial reaction in the gray matter and practically none in the white matter. Del Rio Hortega and Penfield [16] described two types of neuroglial change about experimental brain punctures. The first, in which the cells were undergoing destruction, was characterized by coarse granulation of the cytoplasm and pigmentation of the expansions. The second, leading to typical glial proliferation, was manifested by a swelling of the cell body and fine granulation of the cytoplasm. This stage led to typical direct cell division and to the transformation

12. Coen, E.: Ueber die Heilung von Stickwunden des Gehirns, Beitr. z. Physiol. **2**:107, 1887.

13. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. z. allg. Path. **23**:321, 1898.

14. Penfield, Wilder: Meningocerebral Adhesions: A Histological Study of the Results of Cerebral Incision and Cranioplasty, Surg., Gynec. & Obst. **39**:803, 1924; The Mechanism of Cicatricial Contraction in the Brain, Brain **50**:499, 1927.

15. Penfield, W., and Buckley, R. C.: Punctures of the Brain: The Factors Concerned in Gliosis and in Cicatricial Contraction, Arch. Neurol. & Psychiat. **20**:1 (July) 1928.

16. del Rio Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278, 1927.

from protoplasmic into fibrillary astrocytes. Linell [17] repeated the work of Penfield and his associates and confirmed their observations. He believed that the maximum neuroglial reaction, the purpose of which was to form a barrier between normal and damaged brain tissue, was reached at the end of three weeks.

Practically all investigators are in accord as to the sequence of changes produced when the brain is punctured with a blunt needle. In a narrow degenerative zone about the puncture wound the cellular elements, including the neuroglia as well as the nerve fibers themselves, undergo regressive changes. The débris is subsequently phagocytosed by the developing compound granular corpuscles. Beyond this is a zone in which the glia cells hypertrophy and proliferate, leading to formation of a paracentral gliosis. The absence of connective tissue proliferation and gliosis following the removal of the central core by a hollow needle suggested that the degenerating brain tissue, if left in the tract, is the exciting cause of such reaction.

Pfeifer [18] was probably the first to study the changes in the human brain following needle puncture in an operative attempt to localize cerebral tumors. He concluded that neuroglia played no part in the repair of such wounds, the scar being formed solely by connective tissue. Wilson [19] studied the neuroglial reaction in one case in which ventricular puncture was done six days before death, and another in which six punctures were made from seven to eleven and a half months before death. In the first case he described a central zone of intense cellular reaction, and a more distal zone containing hypertrophied astrocytes. In the second case, in which the wounds were older, similar conditions were present, except that the connective tissue reaction was well advanced while the neuroglial response was less acute. Cone [20] studied the neuroglial reaction to a ventricular puncture made ten days before death. He referred only to the regressive changes taking place in the astrocytes. In a general way we have been able to confirm their observations in studying the tract of a needle puncture made three and a half months before death.

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17. Linell, Eric A.: The Histology of Neuroglial Changes Following Cerebral Trauma: An Experimental Investigation, Arch. Neurol. & Psychiat. **22**:926 (Nov.) 1929.

18. Pfeifer, B.: Zur Diagnose von Hirntumoren durch Hirnpunktion, Jahrb. f. Psychiat. u. Neurol. **28**:323, 1907; Fortschr. d. Med. **27**:24, 1909.

19. Wilson, R. B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75 (Jan.) 1926.

20. Cone, William: Acute Pathologic Changes in Neuroglia and Microglia, Arch. Neurol. & Psychiat. **20**:34 (July) 1928.

Simple Linear Incision.—It seems strange that simple incisions of the brain have not been given more attention than a study of the literature would seem to indicate. Cajal [21] described the neuroglial reaction following simple linear wounds in which no large vessels had been damaged. In these the neuroglia had a radial and tangential arrangement similar to that described about puncture wounds. There was but a minor connective tissue core. The individual astrocytes stained less intensely with gold sublimate, and granulation of the processes occurred, usually first appearing in the sucker foot. Regressive changes of more marked degree took place in the cells immediately adjacent to the wound with the formation of ameboid glia. In other words, simple radial incisions of the cortex with a sharp knife produce changes similar to puncture wounds, resulting in a plane of reaction rather than one about a central core. The small amount of connective tissue present in the wound was probably due to the absence of extensive tissue damage or hemorrhage. The rather active proliferation of glia in the absence of connective tissue suggests the possibility that one is not dependent on the other.

Extensive Brain Wounds.—In addition to simple linear wounds, Cajal also studied extensive ones with contusion and serious hemorrhage. He found that cicatrization resulted largely from mesodermal proliferation and increased vascularization. Outside of the connective tissue scar was a zone of gliosis of varying thickness. The changes in the regional astrocytes appeared to be identical with those of the more simple brain wound. Of especial interest, and a point to which we will call attention later, was the rôle that gross hemorrhage played in the formation of the resultant scar. With a moderate or extensive hemorrhage, liquefaction and phagocytosis of the blood cells outstripped the reparative reaction, and a cyst resulted. The marginal zone of softening came to be occupied with large numbers of compound granular corpuscles. The process of cyst formation seems to limit mesodermal reaction to a narrow zone forming the cyst wall.

Effect of Foreign Bodies.—The healing of brain wounds is often complicated by the presence of foreign bodies. These may compress the brain, as occurs in simple depressed skull fractures, or dislocated bone fragments or other foreign material may be embedded within the brain substance. As we will show in a later section, hemorrhage into the brain substance for all practical purposes acts as a foreign body and influences in a special way the reparative process. In this connection we will summarize the contributions dealing with the neuroglial reaction to experimentally placed foreign bodies either on the surface or embedded within the brain substance.

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21. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vol. 2, p. 727.

Foreign Bodies Placed Outside of the Brain: Penfield found that when a nonirritating substance, such as celluloid, was placed over an intact brain, there was no evidence of a diffuse reaction of the neuroglia except perhaps at its margin where some thickening of the superficial glial layer took place. In this case the reaction to the foreign body was essentially mesodermal. In a series of experimental depressed fractures of the skull with foreign bodies introduced into the extradural space, Naffziger and Glaser [22] found no regional gliosis. This only occurred when the brain itself had been damaged by the force of the blow which produced the fracture. This would lead one to believe that the foreign body itself, carefully placed so as to compress the surface of the brain, is incapable of producing a regional gliosis.

Foreign Bodies Within the Brain: Borst [23] studied the reaction of the brain following the introduction of celloidin blocks into the cortex of rabbits. He believed that the neuroglial elements invaded the foreign body itself, an observation which subsequent investigators have failed to confirm. Farrar,[24] in studying the changes following the introduction of sterile elder marrow into the cortex of rabbits, found that the resultant reaction could be divided into: (*a*) an initial passive period for the first twenty-four hours, (*b*) a subsequent period of proliferation and (*c*) a terminal period, characterized by involutional changes. The first period was characterized by a thickening of the overlying pial membrane with the formation of fibroblasts and phagocytic cells. Only minor regressive changes were found in the cortical elements. The second stage was characterized by a gradual replacement of the hematogenous elements in the foreign body by fibroblasts, the formation of a connective tissue sheath and the gradual phagocytosis of the zone of softened brain tissue. Outside the latter zone, reactive gliosis occurred. The terminal stage of the condition was a complete replacement of the foreign body by mesodermal elements, associated with a surrounding zone of connective tissue. A zone of reactive gliosis finally surrounded the entire mesodermal mass. These observations were confirmed by Morgenthaler,[25] who noted a connective tissue zone separating the regional gliosis from the foreign body.

22. Naffziger, H. C., and Glaser, M. A.: An Experimental Study of the Effects of Depressed Fractures of the Skull, Surg., Gynec. & Obst. **51**:17, 1930.

23. Borst, M.: Neue Experimente zur Frage nach der Regenerationsfähigkeit des Gehirns, Beitr. z. path. Anat. u. z. allg. Path. **36**:1, 1904.

24. Farrar, C. B.: On the Phenomena of Repair in the Cerebral Cortex: A Study of Mesodermal and Ectodermal Activities Following the Introduction of a Foreign Body, Histol. u. histopath. Arb. ü. die Grosshirnrinde **2**:1, 1908.

25. Morgenthaler, W.: Heilungsvorgänge in der Grosshirnrinde des normalen und alkoholisierten Kaninchens nach Einführung eines Fremdkörpers, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:431, 1912.

MATERIAL AND METHODS

The material used in this study was forwarded to us by Dr. A. F. Wagner and Dr. J. H. Schaefer of the coroner's department. All the cases that have been studied clinically have come under our observation. A few of the persons who succumbed within a short time or were killed outright were taken directly to the coroner's morgue. The cases in this series are practically the same as those studied in our previous contribution on the reaction of microglia and oligodendroglia.

Blocks of tissue were taken from selected areas of the brain and were stained by the following methods: hematoxylin and eosin, scharlach R, Mallory's phosphotungstic acid-hematoxylin, aniline blue, silver carbonate method for neuroglia and Cajal's gold sublimate method. While we have selected blocks of tissue primarily from the standpoint of local injury, we have also taken them on occasion from the cortex and underlying white matter at points distant from any gross injury. Our purpose in this has been to observe any possible distant effects of the injury on the astrocytes. We have grouped the various cases from the standpoint of the type of lesion in order to trace the various stages of neuroglial reaction.

NORMAL NEUROGLIA

Astrocytes are classified as fibrous and protoplasmic. In addition, there are individual cells that seem to have characteristics of both. Protoplasmic astrocytes, the normal habitat of which is the gray substance, elaborate no fibrils, and their rather complex branches form an arborization about the cell body. The fibrous astrocytes, on the contrary, have longer and less ramified expansions consisting of fibrils which pass through the cell body. They are found in the white substance and in the subpial layer. In either type one or more large expansions form an attachment to regional blood vessels. The function of these "sucker feet" is now believed to be that of support rather than of nutrition. The cell bodies of both types are about equal in size, and when demonstrated, with either a stain or a metal, have a granular appearance. In degenerative conditions it is an alteration in these probable lipoidal granules that results in the formation of neutral fat. We shall have occasion to refer to changes in these cytoplasmic granules later. Centrosomes are also found, usually at the point of attachment of the sucker foot. The Golgi apparatus has not been demonstrated in adult neuroglia. Coarser round or oval granules, known as gliosomes, occur both in the cytoplasm of the cell body and along the processes. Their eccentric situation in the expansions can probably be accounted for by the presence of fibrils in these structures. Some observers conclude that the gliosomes are of the nature of mitochondria and are responsible for the formation of the fibrils themselves. Del Rio Hortega, to the contrary, believes that this is not the case. The glia fibrils, evidently an integral part of the fibrous astrocyte, apparently serve as strong binding elements for bundles of nerve fibers.

They are also present in the sucker foot, and thereby come into contact with the regional blood vessel. This serves to strengthen their vascular attachment.

The nuclei are round or oval and have a well defined membrane. The chromatin substance is found as finely divided granules. The larger granules usually present in the central portion of the nucleus under certain circumstances become adherent to the nuclear membrane. In the hematoxylin and eosin stain the larger granules are dark purple, while finer, dustlike granules have a pinkish tint. It has been of interest to trace changes in these various structures following injuries.

CHANGES IN NEUROGLIA FOLLOWING INJURY

As has already been intimated in previous studies of this series, the various cellular elements have shown a specific local or general reaction to injury. The reaction of each element depends on its specific function. Previous investigators have shown that the neuroglia undergoes three distinct types of change in the neighborhood of experimentally traumatized brain tissue: (1) regressive changes leading to complete destruction, (2) hypertrophy and direct cell division of more remotely situated astrocytes and (3) a reversible reaction in an intermediate zone in which moderately altered glia cells may be restored to functionally active ones. There are structurally three distinct zones in the region of damaged brain tissue, to which another may be added when the nature of the reactive change is fully appreciated. In the first zone the various elements are damaged beyond recognition, resulting in a more or less homogeneous débris. An immediately adjacent zone of variable width, depending on the degree of injury, is composed of cellular elements and nerve fibers which are doomed to complete destruction. While these are histologically recognizable immediately following the injury, regressive changes soon occur which lead to complete disintegration of the involved structures. Therefore, in the two zones just described, the end-result is probably the same for all types of cells and fibers regardless of their nature or function.

In the third zone, or zone of reaction, the changes occurring in the various individual elements depend on the specific function of each. In this connection we shall confine ourselves to the changes occurring in the neuroglia. From a functional standpoint this zone may be subdivided into two parts. In a rather narrow strip bordering the zone in which all elements are degenerating, the astrocytes undergo a degree of regressive change from which they are capable of recovering. Penfield has aptly termed this process a reversible reaction. The second part of this zone, considerably wider than the first, is characterized by a positive reparative reaction in the neuroglia, manifested by hyper-

trophy and proliferation. These zones are by no means clearcut, particularly in the jagged and irregular contusions and lacerations of the human brain. This situation is also probably influenced by the susceptibility of individual cells, as it is not uncommon to find one or more of them in a restricted area undergoing complete destruction while their adjacent fellows appear to be unaffected.

It is to the first subdivision of the third zone, where reversible reaction occurs, that we wish to direct especial attention in this study. Our observations will be discussed more in detail in later paragraphs.

THE REACTION OF NEUROGLIA TO SPECIFIC TYPES OF BRAIN INJURY

At the risk of appearing to be somewhat didactic, we have chosen to consider changes in the classic neuroglia which follow specific injuries to the brain. Its practicability to the clinical observer is evident, for it is of importance to understand the pathologic changes and ultimate outcome of a given lesion if only from a prognostic standpoint. Furthermore, this information forms a basis for future operative therapy, as has already been emphasized by Foerster and Penfield.[26] By following this plan it will be much easier to compare the various types of experimental injury, from the standpoint of neuroglial change, with those occurring in the human brain.

This problem following head injury will be considered under two headings: (*a*) the neuroglial reaction to specific traumatic lesions, and (*b*) the peculiar changes occurring in the astrocytes in such injuries. The following varieties of injury will be considered: (1) minor cortical contusion; (2) severe cortical and subcortical contusion with hemorrhage; (3) laceration; (4) hemorrhage, both gross and microscopic, and (5) incidental lesions such as local infarctions following fat embolism. In the accompanying table our cases have been classified from the standpoint of gross pathology on the basis of the lesions just enumerated.

Minor Cortical Contusions. — We have chosen to consider minor cortical contusions apart from more extensive ones, as such lesions are probably present in many persons surviving an injury. They are characterized by a discoloration of the cortex alone, with a nominal amount of hemorrhage. The bleeding occurs either as localized petechial hemorrhages, or as rows of blood cells between nerve fibers radiating toward the cortex. Within the involved area of even minor bruising the astrocytes showed an early tendency to fragmentation of their processes, and their cell bodies in some cases were filled with vacuoles (case 13,

26. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

survival period two hours). The cell boundaries were very irregular and the nuclei were small and eccentric. No evidence of direct cell division was observed. In another case (case 6, the patient living about four days after the injury), active direct cell division was taking place at the margin of the bruised area and in the subcortical white matter, with hypertrophy of the reacting cells. The cells in the involved area and about local petechial hemorrhages were undergoing regressive

Classification of Gross Traumatic Lesions

Case	Age	Sex	Survival Period	Gross Lesions
			Cortical Contusions—Minor	
13	10	M	2 hours	Contusion base of both frontal lobes
6	26	M	3 days, 19 hours	Minor contusion left frontal lobe
9	32	M	14 days	Contusion left frontal lobe
			Cortical Contusions—Severe	
19	70	F	Killed outright	Contusion right temporal lobe
1	63	F	¾ hour	Contusion left temporal lobe with petechial hemorrhages
17	84	F	1¼ hours	Contusion basilar surface both frontal lobes
14	75	F	2 hours	Contusion right frontal and right temporal lobes
3	41	M	2 hours	Contusion anterior poles both frontal lobes
5	38	M	6¾ hours	Contusion cortex right temporal lobe
23	30	M	12 hours	Contusion left temporal lobe
11	9	F	26 hours	Extensive contusion left temporal lobe
21	17	F	56 hours	Contusion right and left temporal and right frontal lobes
6	26	M	3 days, 19 hours	Contusion cortex left temporal lobe
25	38	M	21 days	Contusion right temporal lobe
			Laceration	
14	75	F	2 hours	Laceration right frontal lobe
7	14	M	38 days	Severe laceration left temporoparietal region
			Hemorrhage—Gross	
2	29	M	31 hours	Hemorrhage into left temporal lobe
4	51	M	7 months	Old gross hemorrhage right temporal lobe
20	48	M	5 days	Gross hemorrhage into left temporal lobe
			Hemorrhage—Petechial	
19	70	F	Killed outright	Widespread petechial hemorrhages
10	35	M	14 hours	Multiple petechial hemorrhages left cerebral hemisphere
18	35	M	3 days, 3 hours	Generalized petechial hemorrhages
16	67	M	3½ days	Petechial hemorrhages both frontal lobes
6	26	M	3 days, 19 hours	Petechial hemorrhages white matter left frontal lobe
8	22	M	4½ days	Multiple widespread petechial hemorrhages
22	38	M	6½ days	Widespread petechial hemorrhages
4	51	M	7 months	Petechial hemorrhages adjacent to major hemorrhage

change. It was of interest to note that the degree of activity of direct cell division was in inverse proportion to the proximity to the injury. Some very interesting changes were found in the brain of a person (case 9) surviving a minor bruise for fourteen days and succumbing to a complication. Within the central portion of the bruised area, "ghost" forms of ameboid glia were present just outside a zone of phagocytosis. In the zone just outside that in which active destruction was taking place, a peculiar reaction of the neuroglia was observed. Peculiar unipolar and bipolar cells were observed which appeared to be the result of a loss of several cell processes. These cells, suggestive

of "embryonic cells" observed in gliomas, appeared to be well impregnated with gold, as though they were still living forms. Another observation worth mentioning was the overtaking of local double forms by regressive change. In such instances one of the two cells often appeared to be undergoing regressive change with loss of its processes, while the other appeared to be viable. The degree of cellular proliferation was again found to be inversely proportional to the distance from the injured area, being very active in the adjacent zone and becoming less so deeper in the white substance.

While none of our cases showing minor bruising have been followed for more than two weeks, one can anticipate fairly accurately what the end-result will be. The occurrence of phagocytosis in the central portion and the active peripheral glial reaction suggest that the final condition will be a small patch of gliosis with a degree of contraction, which probably does not involve the arachnoid. Small local or regional petechial hemorrhages will probably result in the formation of small cystlike cavities lined with connective tissue and filled with xanthochromic fluid. This particular detail will be discussed later.

Severe Cortical and Subcortical Contusions with Hemorrhage.—It has seemed best to classify cortical contusions as minor and severe, the essential difference being in the size of the bruised area and the additional factor of gross hemorrhage. This factor of gross hemorrhage plays an important rôle in the production of the terminal picture. As the neuroglial changes accompanying hemorrhage are to be described under a separate heading, we shall confine ourselves to a description of these changes in the bruised area. We have included in this heading of severe contusion those cases in which the cortex and subcortical tissue were involved and marked by hemorrhages larger than the usual petechial extravasation. In many of them there was a clot of variable size which had actually replaced the cortical tissue, around which additional smaller satellite hemorrhages were found. Histologically, the lesion was characterized by a breaking up of extensive areas of cortex marked by large hemorrhagic extravasions.

In a rather characteristic manner the changes in the neuroglia might be classified into three types depending on the zone in which the cell chanced to be found. This is in accord with the observations of Penfield and others. The first zone is a rather narrow one found immediately adjacent to the large central or smaller peripheral hemorrhages, and characterized by an almost immediate and total destruction of the astrocytes. It is difficult even in recent cases to demonstrate the remains of such cells in the markedly altered débris. This zone may be made to include the adjacent tissue in which the neuroglia undergoes regressive change leading to complete destruction within the next few days. We have grouped these two zones as *the zone of complete*

regressive change. One may trace in the peripheral portion of this zone typical acute degeneration of the neuroglia, the details of which will be described in later sections. These zones are indicated in figure 1.

A mesial zone may be designated as *the zone of reversible reaction,* which overlaps to some extent the bordering areas on either side. The difficulties in sharply outlining this zone are apparent when it is realized that it is impossible to tell when looking at a cell in any given

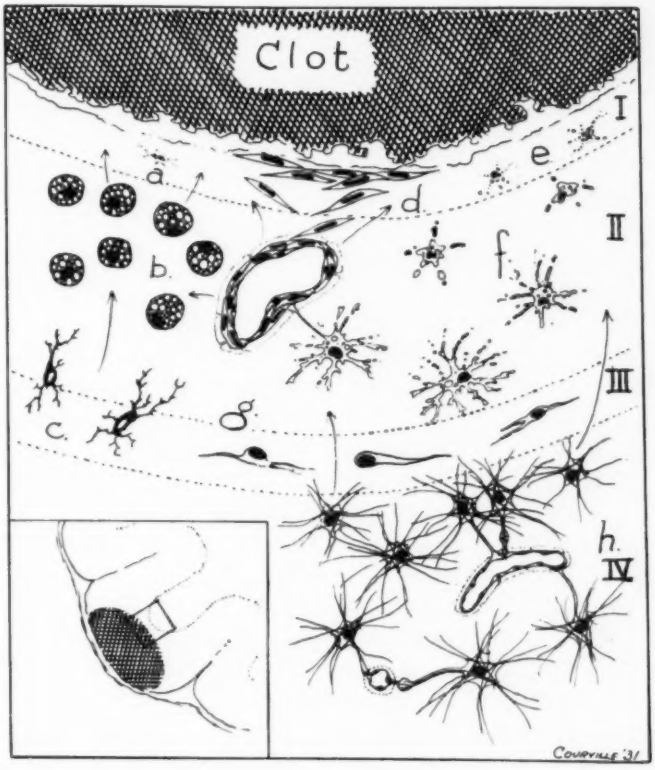

Fig. 1.—Diagrammatic illustration of neuroglial reaction to cortical contusion with hemorrhage (recent stage). The arrows indicate the direction of migration of various cellular elements. The insert shows the area included in the diagram (cortex of temporal convolution). *I* indicates the zone of immediate destruction; *II*, the zone of secondary or delayed disintegration; *III*, the zone of reversible reaction; *IV*, the zone of reactive gliosis; *a*, degenerating mesoglia within the zone of immediate destruction; *b*, compound granular corpuscles in the zone of late regressive change arising from the local mesoglia (*c*), or mesodermal elements of the blood vessel walls; *d*, proliferation of fibroblasts to form a narrow and incomplete zone of connective tissue; *e*, actively degenerating astrocytes; *f*, regressive changes in more distant astrocytes (ameboid glia); *g*, apolar, bipolar, unipolar and multipolar forms of astrocytes undergoing reversible reaction, and *h*, active proliferation of hypertrophied fibrous astrocytes.

stage of the process whether or not it is capable of surviving the injury. As will be subsequently shown, it is possible for a cell to lose many or even all of its processes and still retain its viability. It seems evident therefore that glia cells within this zone can and do regain in time their function and their normal morphologic aspects.

The distal zone, or *zone of reaction*, is characterized by hypertrophy and proliferation of the neuroglia. This region evidently is influenced by the injury only in so much as it serves as a stimulant to cellular activity, and here again the intensity of the reaction is apparently directly proportional to the distance from the injured area. Such zones are to be found most typically in the brain subjacent to the injury. The involved cortex, which is broken up by the contusion and subsequent hemorrhage, undergoes destruction more or less en masse. Destructive changes in such areas are more or less generalized and proceed with the same degree of rapidity. This is due no doubt to the profound disturbance in the cortical blood supply as well as to the original trauma. In one of our cases, however (case 20, with a survival period of five days), in which an extensively bruised area was marked by numerous fairly small hemorrhages, these various zones could be traced microscopically throughout the region. Midway between the various hemorrhagic spots were found comparatively normal astrocytes, while shading off on either side the typical stages of regressive change could be seen.

The essential changes in the development of these zones may be described as follows. There is a gradual widening of the original narrow zone of complete destruction as regressive changes come to involve the adjacent tissues. The astrocytes immediately adjacent to the injury soon lose their processes, and the cell bodies disintegrate. Their disappearance is followed by similar changes in the more peripheral cells for a variable distance, depending on the severity of the injury. This change does not proceed evenly throughout the tissue, for it is not uncommon to find cells undergoing complete destruction in regions where the neighboring astrocytes show little or no alteration. This may be explained either on the basis of a variation in individual susceptibility or on that of an irregular and uneven effect of the injury, possibly through interference with the blood supply. By the end of the first week, and probably within five days, this regressive change has become more or less stabilized, and does not spread to any great extent beyond the limits reached at this time.

The neuroglial reaction which ultimately results in the formation of a glial scar is the response of the uninjured peripheral astrocytes, together with that of more centrally situated cells, which have undergone a reversible reaction to resume their more or less normal activity. This reaction on the part of the neuroglia, as far as we are able to

determine, is a purely local and not a general phenomenon. It was difficult to find unquestioned evidence that direct cell division was taking place more than a few millimeters from the actual zone of injury. This has led us to believe that the neuroglial reaction from the standpoint of injury is a response to tissue destruction, and that as the destruction is local the reaction is local. The neuroglial proliferation is probably excited chemically by the products of disintegration which permeate the adjacent tissue for a limited distance. This would seem to controvert the conception that the remote sequelae of brain injury are due to diffuse general gliosis, a theory which has been held by some clinicians for many years.

Laceration of the Brain.—The conception of lacerations of the brain varies in the minds of clinical and pathologic observers. Every case of severe bruising is undoubtedly accompanied by direct or indirect tearing of tissue, as can be seen in histologic sections. We have considered, however, such minor manifestations to be a part of a contusion, and have reserved the term laceration to describe cases in which gross tearing of the brain has occurred. The latter is typically seen in persons sustaining comminuted depressed skull fractures with damage to the underlying brain. In these cases the greater extent of neuroglial reaction is directly dependent on the greater degree of injury. It is more difficult to make out distinct zones of reaction such as have been mentioned in local bruising. The essential features, as suggested in a person who survived a severe laceration of the brain for thirty-eight days (case 7), may be described as follows: The zone of destruction was much wider and more irregular, and came to be occupied ultimately by a fine reticulum in which nuclei were embedded (fig. 2). Scattered through this reticulum was found a black granular débris, much of which had been engulfed within phagocytes. The nature of these nuclei was difficult to determine, because no cytoplasm was demonstrated about them by the combined method of Penfield or by the gold sublimate, silver carbonate, reduced silver or Perdrau methods. In this zone were found patches of reacting glia and groups of macrophages evidently phagocytosing residual areas of débris. The bordering peripheral zone showed peculiar reactive forms of neuroglia of two essential types. The most conspicuous of the two were large, often multinucleated glia cells which had undergone hyaline change. The second, to be given more attention in later paragraphs, consisted of peculiar apolar, unipolar, bipolar or occasionally multipolar cells, which at first glance resembled the embryonic forms observed in the malignant varieties of the gliomas. Still more peripherally was found an irregular zone of gliosis in which the individual astrocytes had also undergone some degree of hyaline change (figs. 3 and 4).

The course of the changes following laceration may be briefly considered in this connection. The profound injury results in extensive masses of degenerating tissue, which are gradually removed by the macrophages. It likewise seems to result in a delayed and atypical neuroglial response, in which some unknown factor, perhaps an interference in blood supply, results in hyalinization of the reacting glia. The end-result, so well known by those who have had occasion to study

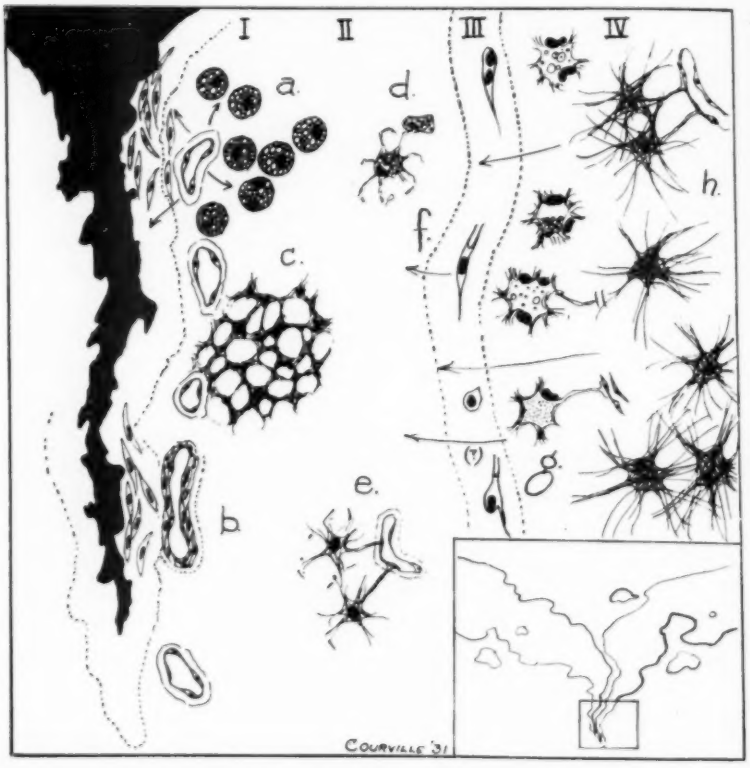

Fig. 2.—Diagrammatic illustration of neuroglial reaction to laceration (late stage). Actively degenerating astrocytes have been phagocytosed and removed. The arrows indicate direction of cellular migration. *I* shows the zone of immediate destruction; *II*, the zone of secondary or delayed disintegration; *III*, the zone of reversible reaction; *IV*, the zone of reactive gliosis; *a*, compound granular corpuscles arising from the mesodermal elements of the regional blood vessels (in white substance); *b*, proliferation of fibroblasts to form bordering connective tissue scar; *c*, filigree meshwork with hyperchromatic nuclei (? of neuroglial nature); *d*, dendrophagocytosis of slowly disintegrating astrocyte; *e*, patches of chronically altered neuroglia; *f*, apolar, bipolar, unipolar and multipolar forms undergoing reversible reactions; *g*, hyalinized multinuclear astrocytes (giant cells) showing regressive changes, and *h*, hypertrophy and proliferation of fibrous astrocytes.

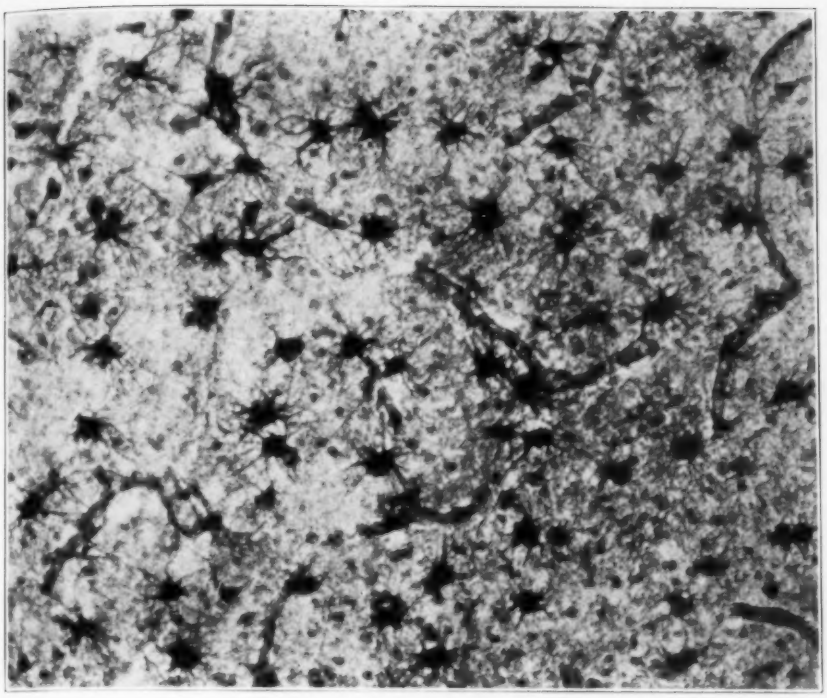

Fig. 3 (case 7).—Reactive gliosis adjacent to a thirty-eight day old laceration. Hypertrophy and direct cell division of astrocytes are shown. Gold sublimate method, × 220.

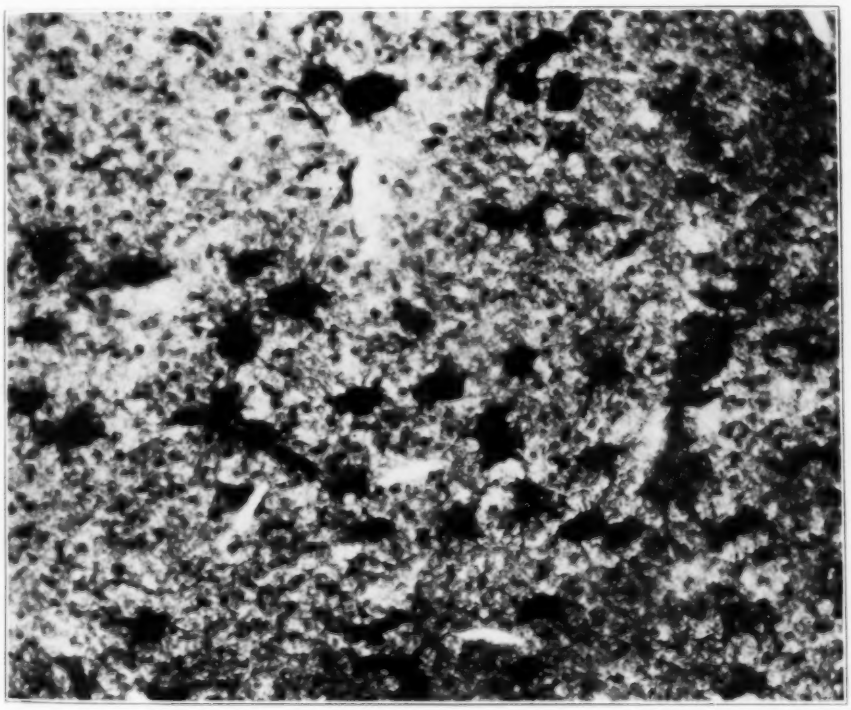

Fig. 4 (case 7).—Hyalinization of reacting astrocytes. The cell body is swollen, and expansions appear somewhat short and frayed out. Gold sublimate method, × 220.

the late effects of brain laceration, consists of a central connective tissue scar and an intense regional gliosis. We have had occasion to study such a case, not included in this series, illustrating this fact. In a child, aged 3, who had sustained a laceration of the right parietal cortex incident to forceps delivery at birth, a linear scar answering this histologic description was found. From this typical end-picture one must conclude that the loose reticular tissue becomes ultimately replaced by connective tissue, and that the atypical and incomplete gliosis is converted into a dense glial cicatrix. The fate of the hyalinized astrocytes and the "embryonic forms" remains an open question.

Neuroglial Reaction to Hemorrhage.—Hemorrhage is a common and often serious result of severe head injuries. The presence of blood in the cerebrospinal fluid is the rule. It would seem that the part played by free blood in the brain tissue from the standpoint of immediate or ultimate change has been given too little attention. Hemorrhages following injury may be classified as follows: (*a*) gross hemorrhages, either in the form of (1) extensive cortical hemorrhages following severe contusion, or (2) true traumatic intracerebral hemorrhages; (*b*) petechial hemorrhages (1) associated with cortical bruising or (2) regional petechial hemorrhages. The latter are incident to local dislocation effects as observed in the corpus callosum or due to severe local injury as occurs in the white matter of a lobe which has undergone extensive cortical bruising. There are, finally, (3) widely scattered petechial hemorrhages either due to sudden changes in the cerebrospinal fluid pressure or resulting from multiple fat emboli.

A few general considerations need to be emphasized before the details of neuroglial changes are described. A local clot or hemorrhage of any size immediately becomes a foreign body as far as the reaction of the surrounding brain tissue is concerned. Furthermore this "foreign body," through the degeneration of the red blood cells, disappears more rapidly than repair can take place, or multiple smaller hemorrhages may so break up fairly extensive portions of the cortex that degeneration en masse takes place.

Gross Cortical Hemorrhage: In any case of severe contusion a clot forms beneath the pia mater which is sometimes of considerable size. In this series we have not been able to trace the neuroglial reaction to its end-stage. Certain early changes have been observed. Judging from what takes place in gross cerebral hemorrhage and from the observations in old injuries of the brain, the lacking details may be supplied.

Any hemorrhage of consequence results not only in the destruction of the brain tissue in the space which it comes to occupy, but also in a zone of softening of the brain tissue at its margin. The glia cells in this zone undergo regressive changes during the first few days after injury, with the formation of ameboid glia cells as an intermediate stage

(fig. 5). The glia cells outside this zone undergo active proliferation, resulting in a zone of gliosis. Rapid degeneration of the red blood cells with subsequent phagocytosis results in the formation of a subpial or subarachnoid cyst, lined by a very narrow zone of connective tissue surrounded by a layer of neuroglia.

Traumatic Cerebral Hemorrhage: The reaction of neuroglia to traumatic cerebral hemorrhage is not unlike that due to other causes, as has been described by Globus.[27] He described three zones about cerebral hemorrhages. In early stages there was a zone of softening,

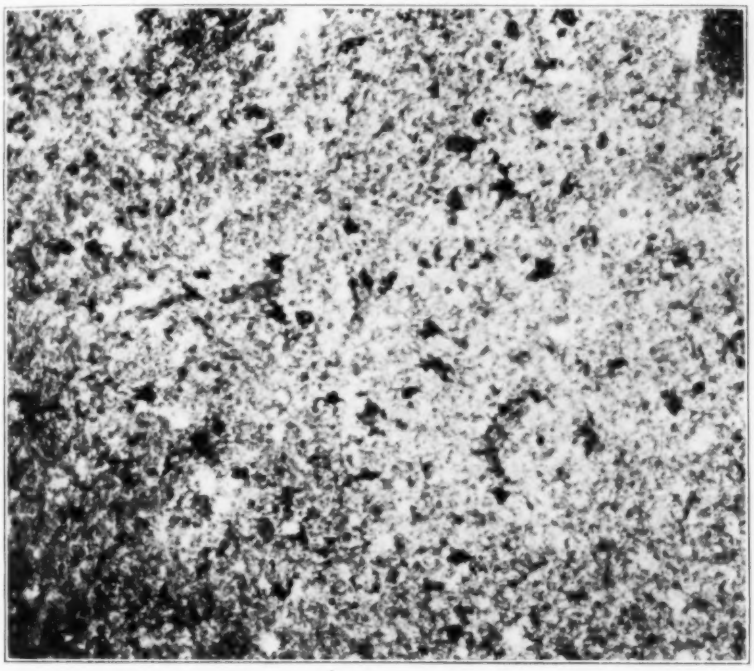

Fig. 5 (case 20).—Degenerating astrocytes at the margin of the small cortical hemorrhage. The various forms of acute degeneration are readily seen. Gold sublimate method, × 100.

a zone of vascular reaction, and finally surrounding this a zone of gliosis. In a later stage there was found an internal homogeneous structureless layer lining the cavity, a middle zone of phagocytes, astrocytes and a network of blood vessels. External to this was a third layer of intense gliosis. In this series we have three examples of gross intracerebral hemorrhage, one of thirty-one hours' duration

27. Globus, Joseph H.: Glia Response in Chronic Vascular Disease of the Brain, Arch. Neurol. & Psychiat. **20**:14 (July) 1928.

(case 2), one of five days' duration (case 20), and finally one of seven months' duration (case 4).

From the standpoint of gross pathology the area about a large intracerebral hemorrhage is marked by a zone of softening in which small petechial hemorrhages are found. Histologically, there is observed a rather narrow zone immediately adjacent to the hemorrhage in which a rapid and complete destruction of all elements occurs. Adjacent to it, in a zone marked by petechial hemorrhages, are to be found typical regressive changes (ameboid glia). Still more peripherally, in what ordinarily would constitute the zone of reaction, certain minor changes, such as vacuolization of the nucleus and cytoplasm of the neuroglia, are observed.

In a person surviving for two days a hemorrhage into the left temporal lobe (case 2), a narrow zone of destruction contained neuroglia undergoing rapid degeneration in which the site of the cell was often marked only by an irregular group of coarse black granules. The second zone was characterized by the presence of vacuolar spaces in the tissues suggesting the presence of local edema. Indicating early regressive changes, the cells in this zone failed to take either the usual stains or metallic impregnations as well as the adjacent unchanged brain tissue. Evidently the first change in this fairly wide zone was the occurrence of local edema and tissue softening, due no doubt to pressure of the expanding hemorrhage and interference with local blood supply. This was also suggested by the presence of petechial hemorrhages. Neither this zone nor the bordering normal tissue gave any evidence of direct cell division on the part of the neuroglia. Of interest in this connection, we have noted in our previous study that direct cell division was already taking place in the microglia in this area.

In case 20, with a survival period of five days, ameboid forms of astrocytes were found immediately adjacent to the large hemorrhage and forming a ring about the petechial hemorrhages. In more distant regions, beginning proliferation was evidenced by swelling and direct cell division of these cells. It may be inferred therefore that in gross hemorrhage the neuroglial proliferation begins sometimes between the second and fifth day. It is this proliferation that leads to the formation of the regional gliosis described by Globus.

In the third case of gross hemorrhage into the right temporal lobe, with a survival period of about seven months (case 4), a late stage of the condition was observed. Three zones could still be demonstrated. There was a narrow, irregular internal zone of connective tissue, a loose reticular zone marked by patches of gliosis and groups of compound granular corpuscles, and a final peripheral zone of incomplete gliosis, marked also by patchy areas of degeneration. The internal zone of connective tissue possibly corresponds to the internal struc-

tureless zone of Globus. This observer fails to state the age of the hemorrhagic cyst which he studied, and makes no reference as to the occurrence of connective tissue.

In a certain number of cases, injuries to the head produce intracerebral hemorrhage. At the periphery of the clot we find the three typical zones as described in other lesions. The essential difference seems to be in the formation of a wider central zone in which regressive changes are accelerated by the occurrence of edema and petechial hemorrhages. In the inner zone complete destruction of all elements takes place, and in the second zone as well the process is more or less complete. Destruction in this wider middle zone is followed by very active phagocytosis and patchy and incomplete gliosis. Glial proliferation is found at the peripheral margin of the second zone with a tendency to invade the mesial zone. The end-stage is a cyst lined by a narrow margin of connective tissue with a subjacent zone of reactive gliosis. This gliosis is undoubtedly accompanied by an increase in the vascular network, as has been mentioned by Globus.

Petechial Hemorrhages: There are evidently numerous factors at work in the production of petechial hemorrhages following head injury. As a result of our investigations it is evident that, with one possible exception, neuroglial reaction following such hemorrhages is the same regardless of the exciting cause. Perhaps the only factor influencing the neuroglial reaction in such instances is the size of the hemorrhage. A small hemorrhage producing little disturbance is not likely to result in any noticeable change in the neuroglia. A petechial hemorrhage large enough to cause regressive changes in the surrounding brain produces rather characteristic alterations, which have been followed in the various survival periods of our series. When bleeding occurs, as for example about a small capillary blood vessel, the expanding hemorrhagic focus often results in its destruction, a tearing loose of the sucker feet, and a concentric compression of the surrounding brain tissue. If large enough, this compression results in local tissue ischemia and softening, attended by consequent regressive changes in the regional neuroglia (fig. 6). These regressive changes take some time to develop, particularly in so far as the glia fibrils are concerned. The phosphotungstic acid-hematoxylin stain revealed no change in these fibrils during the first few days. About the smaller hemorrhages there were condensation and compression of the perivascular glia. About larger local hemorrhages a narrow zone of softening may be found in which typical regressive changes occur. The local astrocytes surviving the insult hypertrophy and in some cases proliferate. Rapid destruction of the red blood cells leaves a small, round, cystlike space surrounded with more or less actively proliferating glia. Such proliferative changes

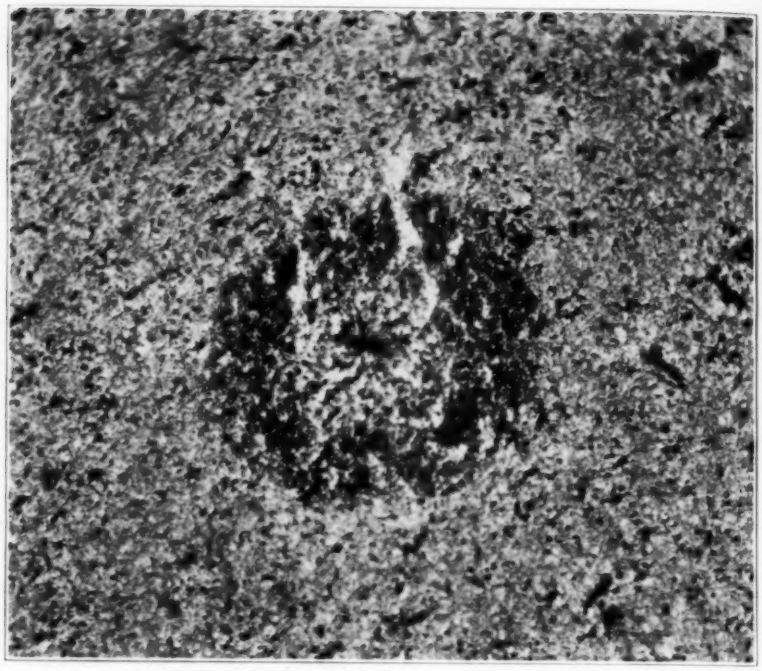

Fig. 6 (case 20).—Petechial hemorrhage (survival period of five days) with degeneration of regional astrocytes. Gold sublimate method, × 100.

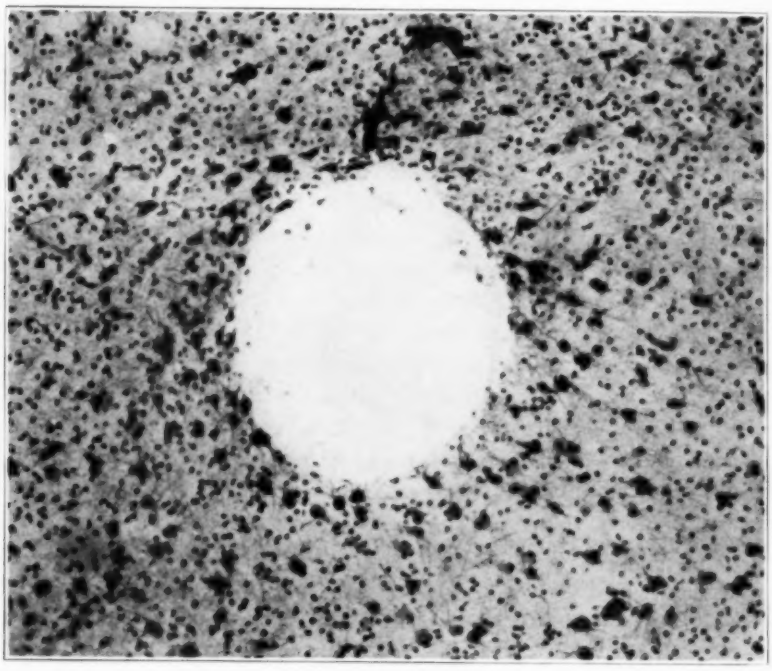

Fig 7 (case 4).—Petechial hemorrhage (survival period seven months). The tendency to gliosis about the subcortical petechial hemorrhage is shown. Silver carbonate method, × 100.

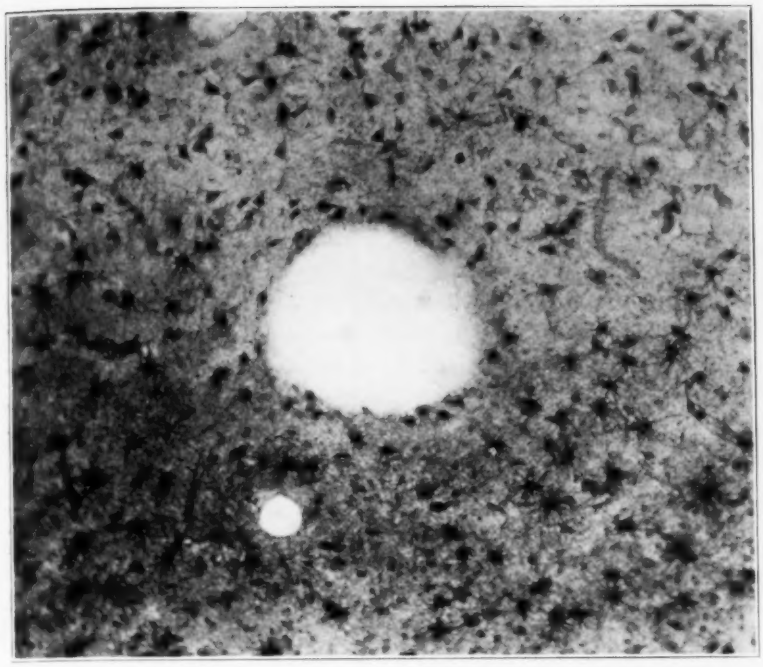

Fig. 8 (case 4).—Smaller petechial hemorrhage between the cortex and white substance. The active gliosis in the white matter stands out in contrast to the retarded glial reaction of the cortex. Gold sublimate method, × 100.

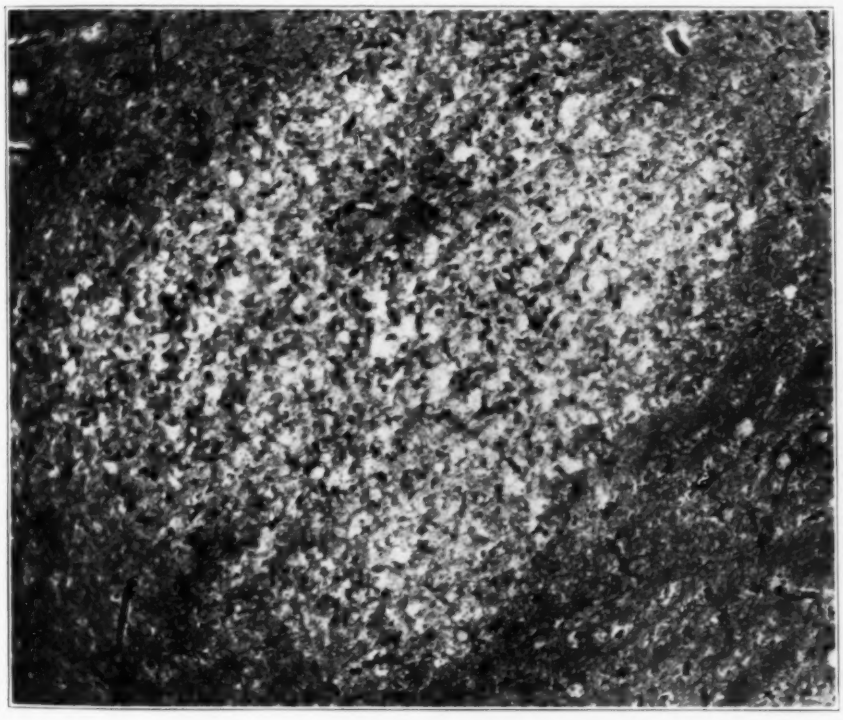

Fig. 9 (case 8).—Acute regressive changes in the neuroglia in an infarcted area following fat embolism. Gold sublimate method, × 100.

may ultimately result in a more or less complete ring of gliosis (figs. 7 and 8). A further word should be added in regard to the changes in petechial hemorrhages following multiple fat emboli. It is recognized that cerebral fat embolism is in most cases not a result of head injury but is secondary to fracture of some long bone. Multiple small infarctions with or without hemorrhages are to be observed. These infarcted areas, as seen in case 8, show typical ameboid changes in the neuroglia (fig. 9). While we have not had the opportunity to study late changes consequent to fat emboli, it is not unreasonable to believe that focal gliosis would occur if the survival period were long enough.

CHANGES IN INDIVIDUAL ASTROCYTES FOLLOWING HEAD INJURY

The first part of this contribution has been concerned primarily with a description of the general neuroglial reaction to the various types of brain lesion following injury. In this portion of our study we shall discuss the changes taking place in the individual astrocytes. We shall consider first of all the various types of (*a*) regressive change, (*b*) what constitutes a reversible reaction and (*c*) proliferation of glia. We shall consider incidentally the problems of localized and generalized gliosis.

Regressive Changes.—Changes in astrocytes following various types of toxic, infectious or destructive lesions of the brain have been described for many years. Eisath [28] was one of the first to describe detailed acute changes in the neuroglia which gave rise to an ameboid appearance of the cell. He found that the cell became swollen, its nucleus became hyperchromatic, and fragmentation of its processes occurred. Alzheimer [29] paid particular attention to the occurrence of granules within such cells staining specifically with acid fuchsin, methylene blue (methylthionine chloride, U. S. P.), and light green, as well as certain vacuolar spaces found to be filled with fat. The latter he believed to be formed by a gradual enlargement of fuchsinophil granules. He believed that these granules were formed as the result of regressive changes in the cytoplasm. Wohlwill [30] described ameboid forms in vascular lesions, and considered them to be of a regressive nature. Some observers believed that in certain instances

28. Eisath, G.: Ueber normale und pathologische Histologie der menschlichen Neuroglia, Monatschr. f. Psychiat. u. Neurol. **20**:1, 1906.

29. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgangen im Nervengewebe, Histol. u. histopath. Arb. ü. die Grosshirnrinde **3**:401, 1910.

30. Wohlwill, F.: Ueber amöboide Glia, Virchows Arch. f. path. Anat. **216**:468, 1914.

they were the result of postmortem change. Cajal[31] designated the process of the fragmentation of the expansions as clasmatodendrosis. At the time of these earlier investigations, some difficulty was encountered in distinguishing them from compound granular corpuscles. This confusion was due to the fact that both frequently showed short, stubby processes and globules of fat. It remained for del Rio Hortega,[32] with the use of specific metallic methods, to distinguish clearly the ameboid glia on the one hand from the phagocytic mesoglia on the other.

Acute regressive changes in the neuroglia following injuries to the brain are not unlike those produced by other causes. A detailed consideration of these changes is unwarranted at this time, as they have been so well described by other investigators. It will be sufficient to describe certain changes and the sequence of their appearance following trauma. It has been recognized since the time of Alzheimer and Wohlwill that the alterations vary according to the speed with which the process takes place. We shall describe two rather characteristic appearances.

Rapid Degeneration: In the narrow zone bordering the contusion or hemorrhage, all histologic elements undergo almost immediate dissolution. In these areas degenerating glia cells are manifested by an irregular clump of large granules which still attract the gold sublimate stain, or at times by a faint outline of finer granules ("ghost forms"); sometimes a combination of these appearances may be observed with dark irregular splotches superimposed on an outline of fine granules. These granules probably represent an agglutination of the smaller auriphilic granules now made particularly prominent by loss of nucleus and cell wall. In the phosphotungstic acid-hematoxylin preparations the details of nuclear destruction and dissolution of the cell wall may be seen. Large clearcut purple, and clumps of narrow irregular brownish, granules may be seen with this method. These granules undoubtedly correspond to those described by Alzheimer in his various aniline dye preparations. This acute process may be described as destruction of the cell more or less *in toto*.

Slower Regressive Changes (Ameboid Glia): Peripheral to the narrow zone of complete destruction there is an area of varying latitude in which regressive changes take place more slowly. In general,

31. Ramón y Cajal, S.: Contribucion al conocimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:255, 1913.

32. del Rio Hortega, P.: Sobra la verdadera significion de las celulas neuroglicas llamadas amiboides, Bol. r. Soc. españ. de biol. **8**:229, 1918; El "tercer elemento" de los centros nerviosos: I. La microglia en estado normal; II. Intervencion de la microglia en los procesos patologicos; III. Naturaleza probable de la microglia, ibid. **9**:69, 1919.

it may be said that the speed with which the process occurs is directly proportional to the proximity of the cell to the point of injury. A typical picture as seen in the gold sublimate preparation will be described. Adjacent to the margin of the injured tissue the astrocytes had lost all of their processes, and only small streaks and irregular masses of

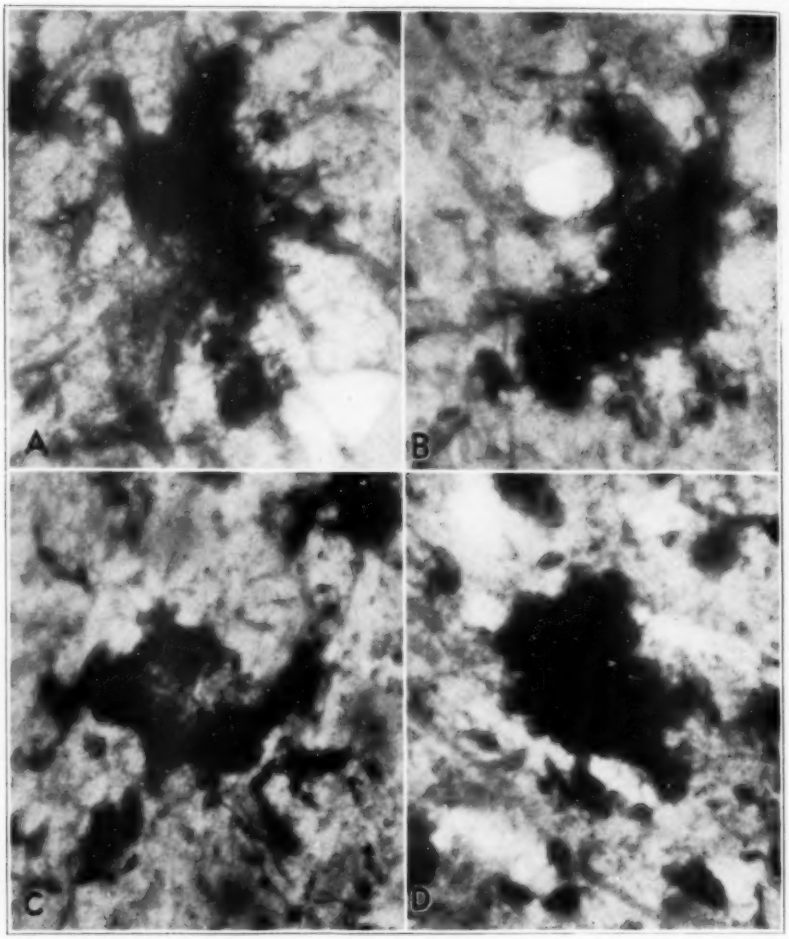

Fig. 10.—Stages in acute degeneration in astrocytes: *A*, granulation of terminal expansions; *B*, loss of terminal expansions; *C*, breaking off of major process; *D*, loss of major processes giving the cell an irregular ameboid appearance. Gold sublimate method, × 1500.

granules in the region of the cell indicated where the cell body had been. Somewhat more peripheral to the injury the expansions were a little longer, and their outlines were sometimes marked by rather coarse granules. Still more peripherally the cells had lost their terminal radi-

cals. In the adjacent zone the cells appeared quite normal in outline, and the only evidence of regressive change was the presence of occasional vacuoles in the cytoplasm. Figure 10 shows these various stages of degeneration. As has been previously intimated, regressive changes do not involve all cells alike in the same area, and it is not uncommon to observe certain portions of the same cell undergoing regressive change while others appear quite viable. Furthermore, in cases with a longer survival period, regressive changes have not infrequently been seen in cells which have appeared to be hypertrophied and undergoing proliferation.

The details of this regressive change can best be studied by comparing a variety of stained and impregnated preparations. There are two fundamental changes to be observed in the cytoplasm, the formation of vacuoles and the development of large granules. What appeared to be vacuoles in ordinary methods proved to be free fat when stained with scharlach R. These vacuoles vary considerably in size and number, depending on the proximity of the cell to the injured area and the speed with which regressive change was taking place. They may be found in cells which otherwise appear normal. The presence of fat is probably to be explained by a breaking down of the complex cellular lipoids into neutral fat.

Coincident with this process, certain changes occur in the chemistry of the cell which favor the agglutination of granules normally present, or their transformation into those of another character, as earlier investigators have already shown. Such granules appear to be of acidophilic and basophilic character. We have not attempted to stain these cells with the various methods utilized by Alzheimer and his contemporaries, as the changes in the ameboid forms are very much alike. We have noticed three varieties of granules which seem to be foreign to the normal cell. The first is demonstrated by the silver carbonate method. Large, round or oval, black granules, usually not more than five or six in number, were observed in cells at some distance from the injury. They were particularly numerous and well developed in the subpial astrocytes. These may correspond to the large granules demonstrated by the gold sublimate method, and, as previously intimated, may be due to an agglutination or coagulation of the normally present fine auriphilic granules. With the phosphotungstic acid-hematoxylin stain two types of granules are observed. One is a large, round or oval, deep purple granule scattered throughout the cytoplasm, which may be identical with those impregnated by the gold and silver methods. In addition, there are often seen irregular clumps of brownish granules in the cytoplasm or the nucleus. Perhaps the only conclusions that one is warranted in drawing are that such granules are evidence of

regressive change, that they are in some way due to alterations in normal cellular constituents, and that there are probably several varieties having different chemical characteristics.

Nuclear changes may be included under the terms pyknosis, karyolysis and karyorrhexis. These changes are particularly well seen with Mallory's method. In regions adjacent to the injury, rupture of the nuclear membrane, hyperchromatosis and irregular arrangement of the chromatin material may be seen. Vacuolization of the nuclei may be found even at a distance from the seat of injury, and may be a part of a general tissue edema rather than a regressive lipoidal change.

The breaking off of the cell processes (clasmatodendrosis) may be an early or late change, depending on the location of the cell. Near the injured area the cells may have lost many or all of their expansions, while those at a greater distance show less marked changes. Coincident with the loss of expansions, vacuolization and granular changes, there is a swelling of the cell body giving rise to the typical appearance of ameboid glia. We were unable to observe dendrophagocytosis, except in cases with a reasonably long survival period. It seems evident, therefore, that loss of processes is not due in the acute stages to phagocytosis by the mesoglia.

Reversible Reaction of the Neuroglia.—Penfield and his co-workers have frequently made use of the term "reversible reaction" in describing cells undergoing regressive change. The implication is that such elements are undergoing alterations of morphologic, biologic and chemical nature, which if continued would lead to the death of the cell (necrobiosis). Some of these cells, however, survive, and are presumably capable of resuming normal function in a certain period of time. The characteristics of cells capable of regeneration, the time periods necessary for the change, and the stages through which they pass have to our knowledge never been described.

Not infrequently, certain unusual cell forms have attracted our attention and deserve consideration. It is understood *a priori* that cells showing changes from which they are capable of recovering will be found in an area between the zones of characteristic proliferation and characteristic destruction. In several cases in which tissue destruction had taken place, we have observed certain apolar, unipolar and bipolar cells which are impregnated by the gold sublimate method, but which also may be demonstrated by any method that shows the cytoplasm of the cells (fig. 11). They were particularly characteristic in case 21 (survival period of about fifty-six hours), and case 7 (survival period of thirty-eight days). In case 21, the blocks were taken from a contused area in the right temporal lobe. These peculiar cell forms were of especial interest in that they suggested a method of their development. In the zone midway between

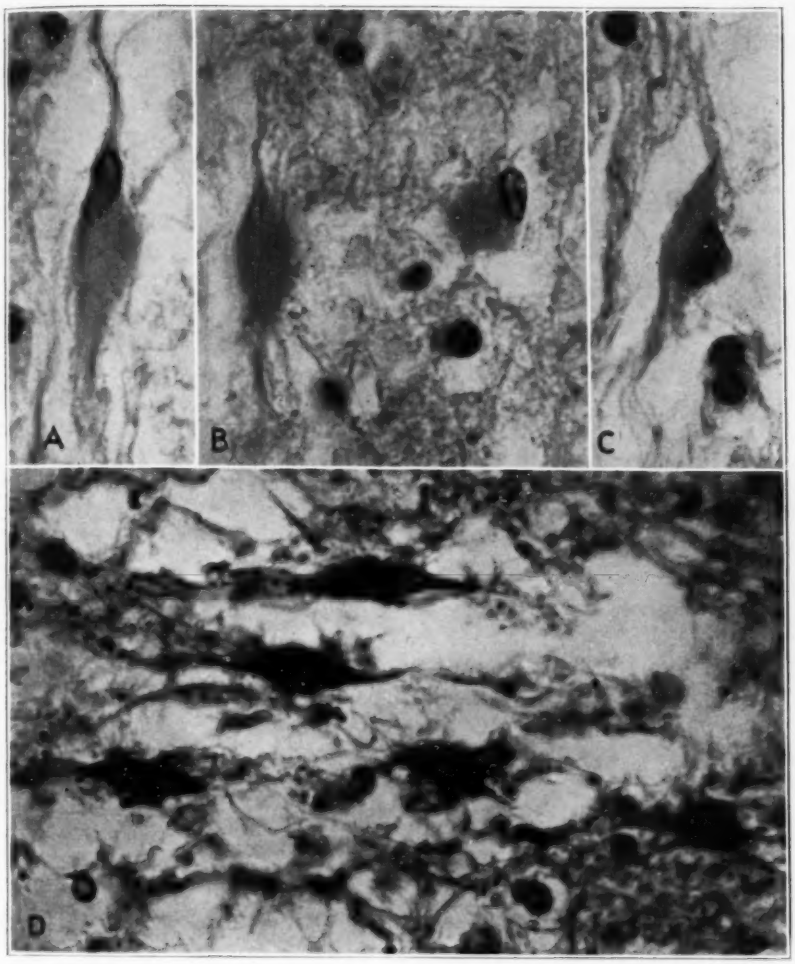

Fig. 11 (case 7).—Morphologic changes in astrocytes indicative of reversible reaction as shown by routine methods. *A*, *B* and *C* shows the apolar, polar and bipolar forms that have undergone some degree of hyaline degeneration. Hematoxylin and eosin, × 800. *D* shows the unipolar and bipolar forms. Aniline blue method, × 800.

the areas of degeneration and of reaction, the glia cells were found to be losing some of the major processes, while one, two or occasionally three processes retained their normal morphologic aspects except for a loss of the terminal expansions. The expansions which were undergoing regressive change attracted the gold less avidly, and their faint granulation stood out in contrast to the deeply impregnated fairly normal processes. Some cells had lost all of their processes and remained as small round or oval forms, which attracted gold sublimate with the same degree of intensity as did the more normal forms in the locality (fig. 12).

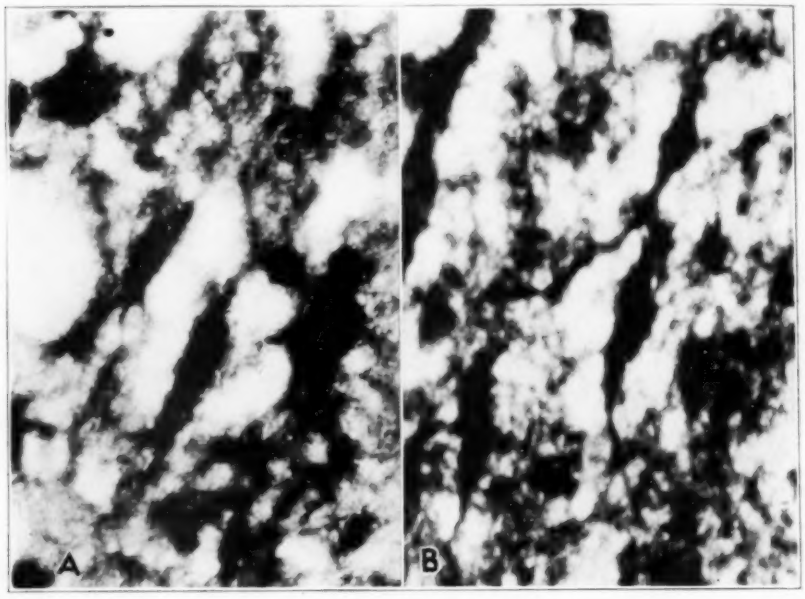

Fig. 12.—*A* (case 7) shows the apolar and bipolar forms of astrocytes. Gold sublimate method, × 800. *B* (case 21) shows the unipolar and bipolar forms. Gold sublimate method, × 800.

In case 7, that of a boy, aged 14, who survived for thirty-eight days an extensive laceration of the left parietal lobe, similar forms were seen. As a matter of fact, it was in the sections taken from an area adjacent to the laceration stained by Mallory's method that we had occasion to observe these peculiar forms for the first time. They were obviously older and presented a more regular contour than those seen in case 21. Apolar, unipolar and bipolar cells were fairly common, many of them having double nuclei. The development of these elements, such as was traced in case 21, was not observed, probably because the process had temporarily become quiescent. The gold subli-

mate preparations showed morphologically identical cells in this zone which lay interposed between the zone of complete destruction and that of reaction. These cells were in part undergoing a hyaline change similar to that of the reacting glia in the adjacent zone. Figure 13 illustrates the immature (case 21) and mature (case 7) forms of these cells.

The significance and mode of formation of these hitherto undescribed elements are of considerable interest. As observed in case 21, the fact seems to us fairly well established that these elements are the result of a breaking off of a variable number of expansions. In individual cells one or more of the polar expansions were deeply impregnated with the gold, while the lateral ones were only lightly impregnated and often appeared to be undergoing granular degeneration. The end-result of the process is a cell only slightly shorter than the transverse diameter of the original astrocyte. It may be argued by some that such elements should be considered as degenerating forms and incapable of recovery, in other words, as dying cells. The intensity of metallic impregnation, the absence of extensive vacuolization, and the occurrence of active direct cell division all speak for their viability. Their position, in a zone bordering on that of active proliferation and outside of the zone of complete necrosis, in itself suggests a possibility of reversible reaction. If these morphologic elements have been properly interpreted, they furnish a tangible demonstration of the method of reversible reaction. By proliferating new processes the typical adult form may be reestablished.

One is tempted to theorize on a possible explanation for the phenomenon. In the embryonic development of the glioblast are bipolar and unipolar transitional stages. These original expansions may for our purpose be designated as primary. Later in its history other, secondary expansions are proliferated, and the cells develop into their typical stellate shape. It is possible that the secondary expansions are more susceptible to injury by various noxious influences and consequently may be the first to be lost. With these processes removed the cell regains its embryonic appearance, and possibly to some extent its embryonic propensities.

The development of these peculiar morphologic forms is evidently due to a large extent to the direct effect of the injury. It was observed, however, especially in the older cases, that such cells usually lay with their long axis parallel to the margin of the injured area. This would suggest the possibility that concentric pressure radiating from the center of injury also had something to do with their shape.

The resemblance of these elements to those seen in the embryonal gliomas brings up the question of the etiologic relationship of trauma to new growth. The occurrence of similar forms following brain injury suggests the possibility, perhaps remote, that these elements

under certain conditions might assume neoplastic tendencies leading to the formation of glioma. Perhaps of still greater significance, this process furnishes a possible modus operandi in the development of gliomas from morphologically typical astrocytes, in contrast to the cell rest theory of Cohnheim. The matter deserves further consideration.

The circumstances under which we were obliged to conduct this investigation have limited our study to that of cellular morphology

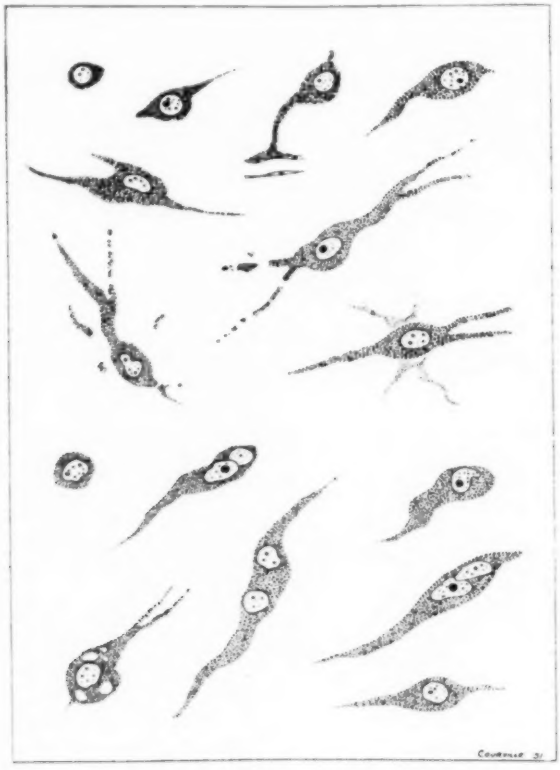

Fig. 13.—Diagrammatic drawings of "embryonic forms" of astrocytes. The cells in the upper part of the figure are from case 21 (survival period of fifty-six hours). These forms are the result of breaking off of secondary expansions. The cells in the lower part of the figure are taken from case 7 (survival period of thirty-eight days). They have a more regular appearance and often contain two nuclei.

demonstrated by the various staining and impregnation methods. We can only surmise, therefore, the physicochemical aspects of the problem. It has been known for some time that the protoplasm of cells could be coagulated mechanically. In such instances the normal granules (colloids) of the cell become swollen and opaque. It furthermore seems very likely that coagulation produced by mechanical as well as by

chemical factors may be a reversible process. It is possible that the increase in size of the auriphilic granules in these injured cells, as demonstrated by the gold sublimate method, is a manifestation of this process.

Adapting this conception to the situation at hand, the cells immediately adjacent to the injury undergo such an extreme degree of mechanical coagulation that regeneration is impossible, and they soon disintegrate. Those somewhat more distant are less severely affected and the process may be reversible. If certain of the secondary processes are more susceptible to injury, they may be destroyed with the formation of the peculiar "embryonic forms" just described. The conception opens up a new field for study of brain injuries from an experimental standpoint.[33]

THE PROBLEM OF GLIOSIS FOLLOWING TRAUMA

In previous paragraphs we have considered the zone of complete destruction and the zone of reversible reaction, as concerns the neuroglia. A consideration of the third zone of reactive proliferation, which ultimately leads to the formation of the glial scar, is now in order. Gliosis is a result of a proliferation of fibrillary astrocytes. We shall discuss its possible causes, its mechanism and its function, as well as its relation to the production of clinical symptoms.

Causative Factors.—Judging from the many conditions in which gliosis occurs, it is evident that there are many factors that lead to its production. From our observation gliosis following trauma is a local manifestation, and the possibilities of impaired blood supply, of general toxic substances or of generalized regressive changes as causative factors may be dismissed without further word. Local gliosis following trauma occurs only when there is destruction of tissue, and the intensity of the glial reaction in the zone of proliferation is in direct proportion

33. All of the tissue used by us in this study was taken from bodies which had been embalmed soon after death. After removal from the skull, the brain was immersed in a diluted solution of formaldehyde, U. S. P. (1:10) until needed. It is evident that this process of chemical coagulation of the cell colloids made a critical study of mechanical coagulation in the various cellular elements quite impossible. We were limited to a comparison of the size of the granules in the injured with those of normal cells. Marinesco made some very interesting observations on mechanical coagulation of the colloids of nerve cells (Kolloid-Ztschr. **11**: 207, 1912; III Cong. internat. de neurol. de psychiat., 1913, p. 20. From a more purely biologic standpoint, the literature dealing with this problem has been recently reviewed by Bancroft and Richter (The Chemistry of Anaesthesia, J. Phys. Chem. **35**:215, 1931). The effect of injury on the cytoplasm of neuroglia must of necessity be investigated experimentally. More fruitful and more important results would be gained, however, if attention would be directed to the nerve cell rather than to the astrocyte.

to the proximity of the reacting cells to the injury. It must be concluded therefore that injury is the exciting factor of the process. It is very likely that the degenerating tissue furnishes a chemical stimulant which diffuses with diminishing effect through the adjacent undamaged tissue. Once begun, neuroglial proliferation continues until ultimate complete repair of the damaged area by a glial scar is accomplished.

The Mechanism of Gliosis.—Unfortunately, it has not been our opportunity to study all the transitional stages in the development of a glial scar. The details of the process have been shown experimentally by Penfield and his collaborators. It is the result of an active proliferation of cells in the zone of reaction, with the possible addition of cells in the adjacent zone undergoing reversible reaction. As Penfield has already described, in simple experimental brain wounds it is possible that a transition may take place by which protoplasmic astrocytes are transformed into those of fibrillary type. In local injuries to the human brain the cortex containing the protoplasmic astrocytes is usually extensively damaged. This may be the reason why we were unable to observe this transition, but in such cases it may be questioned whether these transformed cells play a very important rôle in the formation of the ultimate glial scar. In one instance (case 9, with a survival period of fourteen days) we observed groups of fibrillary astrocytes which may have developed from those of protoplasmic type.

Proliferation of astrocytes in our material took place only by direct cell division.[34] In case 21 (with a survival period of fifty-six hours) and case 6 (with a survival period of ninety-one hours) the astrocytes were undergoing direct cell division, and transitional forms of all stages could be observed. We are unable to state from our observations, dealing as we are with so widely varying factors in different cases, just when the process reaches its maximum. Judging from case 7 (with a survival period of thirty-eight days), in which gliosis was still very incomplete, the process may be frequently very much delayed. This is probably due to two factors. First the severe local shock is met with a feeble though prompt response. Further-

34. Current investigations by one of us (Dr. Courville) seem to indicate that direct cell division of astrocytes is constantly taking place in normal cerebral tissue. If this is true, local glial proliferation following trauma is to be interpreted as an acceleration of a normal process. The occurrence of occasional twin cells or double nucleated forms, observed in the tissues of persons surviving injury but a few hours, cannot therefore be considered as *prima facie* evidence of active response of the neuroglia. Only when numerous enough to exceed the normal state can the appearance of such forms be considered as pathologic. The neuroglial reaction is slower in responding to injury than the microglia or the oligodendroglia, in which changes are to be observed within a few hours after injury.

more, the process seems to be greatly retarded by the actual presence of degenerating tissue, phagocytosis of which is the important work of the moment. This would delay the formation of the ultimate glial cicatrix for a matter of months or even of years. The age of the patient probably has some influence on the speed and intensity of this neuroglial reaction, but from our observations we are incapable of determining its importance.

As to the details of cell division, but few words need be said. It begins with a swelling of the cell body, frequently accompanied by a loss of granulation about the nucleus. There are indentation and constriction of the nucleus, followed by the interposition of an intervening wall. The chromatin material is divided into more or less equal portions within the two daughter nuclei. Under ordinary circumstances nuclear division is attended by division of the cytoplasm and expansions, so that two symmetrical cells result. When the process of gliosis is retarded in the presence of extensive degenerating changes, hyalinization of the proliferating glia takes place and atypical amitosis occurs. In forms to be described in later paragraphs, atypical indentation, constriction and multinuclear elements were observed, not unlike the giant cells so frequently seen in glioblastomas. Such forms have also been described by del Rio Hortega, and Penfield and Cone in experimental brain injuries.

Regressive Changes in Reactive Neuroglia.—Regressive changes occur not only in astrocytes within the damaged area, but also in those at its margin. It is not unusual to see hypertrophied and proliferating glia being overtaken by regressive changes. In addition to these rapid changes, when the process of reactive gliosis is retarded for any length of time owing to extensive tissue damage, many of the hypertrophied astrocytes undergo hyaline degeneration. This change gives rise to peculiar and atypical forms of ameboid and reactive glia. The cells appear swollen, and the cytoplasm has a peculiar homogeneous ground glass appearance when sections are stained by Mallory's method. In gold sublimate preparations the cell body has a slate blue color. In many cells the expansions are broken off, giving rise to very irregular, ragged "coast line" appearances. In others, many of the expansions are preserved. Many unusual and bizarre pictures are thus presented. Variously sized and irregular vacuoles are often present. They may occur as perinuclear halos, as a lacelike meshwork in restricted portions of the cell, or as discrete and somewhat scattered spaces. Peculiar granules or inclusion forms are also observed. Small round or oval dark purplish granules, larger purplish crescents, or small diplococcoid forms enclosed within vascular spaces are commonly observed. Peculiar color patterns, with clumps of purplish granulations surrounded by a

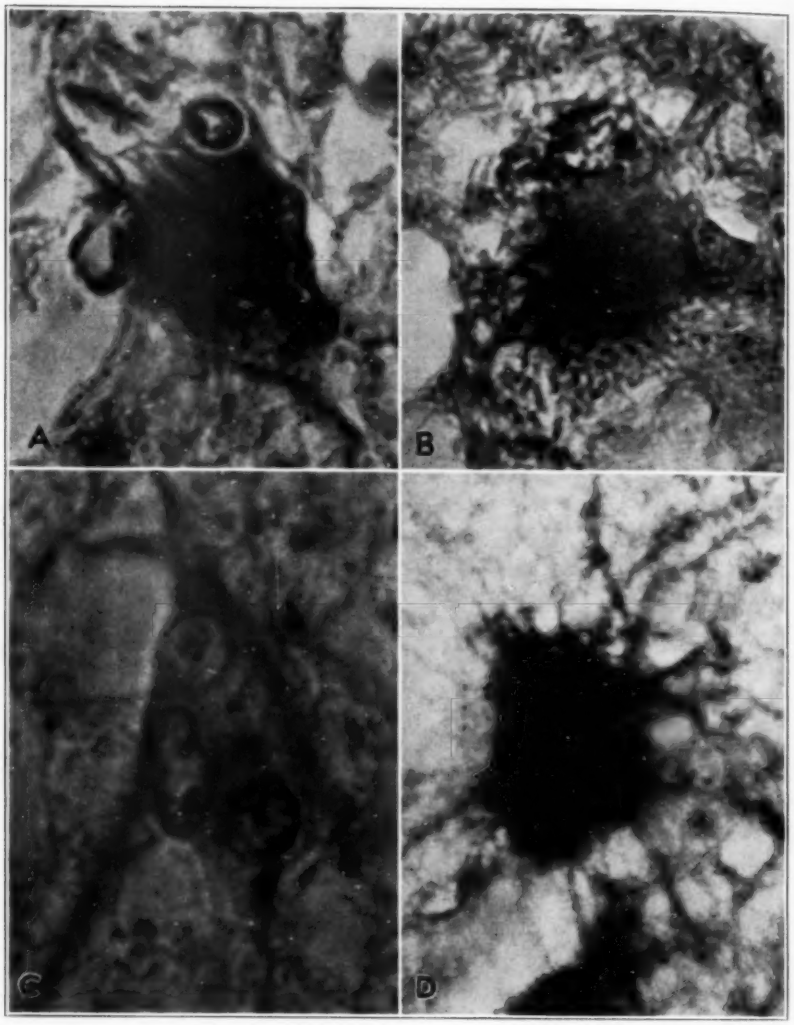

Fig. 14.—Regressive changes in the reacting neuroglia. × 1500. *A* shows a hyalinized astrocyte with ground glass appearance of the cytoplasm. The nuclei are crowded to the periphery of the cell, one showing a large vacuole and another a perinuclear halo. The lower pole of the cell shows a meshwork of small vacuoles. Aniline blue method. *B* shows the formation of granules within the cytoplasm enclosed within small vacuoles. The granules are also seen in the degenerating peripheral portions of the cell. Phosphotungstic acid-hematoxylin. In *C*, an astrocyte with double neuclei and granulation and vacuolization of the cytoplasm are seen. The large vacuole has a clump of central granules. Hematoxylin and eosin. *D* shows a hyalinized cell as seen in the gold sublimate preparation.

pink halo, are often observed. Mallory's aniline blue method reveals red and blue granules in the nucleus, frequently associated with a large round reddish-purple structure surrounded by a clear halo. The nuclei are also frequently vacuolated. About some of the cells is often seen an irregular mass of débris, evidently broken up processes or degenerated portions of the cell body itself, which stain purple with the aniline blue method. Figure 14 illustrates some of the more common types of regressive change. The appearance of such hyaline changes takes place only after an interval of some weeks (case 7, with a survival period of thirty-eight days) and is possibly due to an impaired blood supply.

The Replacement Function of Neuroglia.—As is the case with the other interstitial elements of the central nervous system, the glia cells have a definite kinetic as well as static function. In their normal state this function is largely a passive one. With the network of blood vessels they form the supporting structure of the brain, the "vasoastral framework" of Penfield. Following tissue damage the glia cells actively proliferate to form a glial scar, corresponding in this respect to connective tissue elsewhere in the body. In the end any extensive damage is replaced by the neuroglial cicatrix, by connective tissue, and, in some instances, by the accumulation of fluid. Reduced to its simplest terms the neuroglial scar may be said to have a space compensating function.

THE PROBLEM OF GENERALIZED GLIOSIS

Echoing perhaps an impression of the layman that a person sustaining a severe injury to his head is never the same thereafter, there has been a more or less subconscious notion among medical men that trauma results in generalized gliosis. The problem presents itself in this connection, considering, as we are, the neuroglial reaction to injury. As we have not had the opportunity as yet to study the *late* general effects of injury to the brain, we can only presume what these might be, judging from the more acute lesions. General gliosis could necessarily take place only in the presence of some generalized tissue change, as occurs in syphilitic or arteriosclerotic disease. While it is recognized that general changes do occur following injury, these are due chiefly to a disturbance in the balance between the blood and cerebrospinal fluid (edema). It may well be questioned whether glial proliferation is thus stimulated.

Our observations render this conception unnecessary in explaining the late sequelae of brain injury. We are therefore in accord with the observations of Neubürger and Braunmühl[35] who found local tissue

35. Neubürger, K., and Braunmühl, A. v.: Hirnverletzungen in Anatomie der Psychosen, Handbuch des Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 12, p. 321.

damage in the form of hemorrhagic extravasation, glial scar and cysts. In addition to the easily recognizable cortical and subcortical injuries, we have found small localized injuries in the cortex or in the subcortical white matter (fig. 15). These areas were often more or less devoid of normal nerve cells and fibers, and if the lesions were old enough, local glial proliferation occurred. In addition to such lesions, we have but to recall the changes following petechial hemorrhages of the centrum ovale with miliary cyst formation and ring gliosis. We think that the occurrence of extensive focal cortical damage, together with multiple

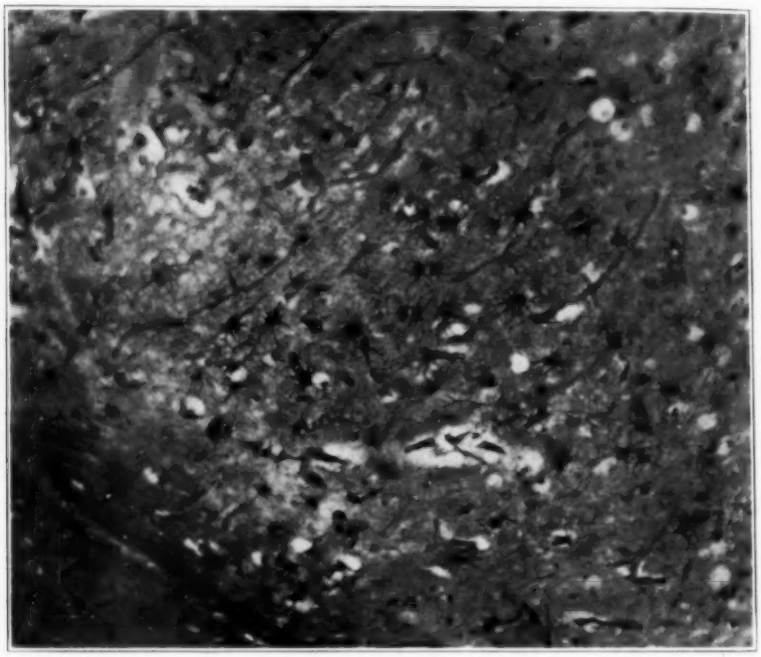

Fig. 15 (case 9).—Small patch of hypertrophied and proliferating astrocytes in the cortex of the left parieto-occipital region, in a patient suffering a severe contusion of the right frontal lobe. Gold sublimate method, × 110.

distant cortical injuries, would account for considerable interference with the function of nerve cells. Furthermore, the frequently associated subcortical injury, together with multiple and often widespread foci of glial proliferation and cyst formation following petechial hemorrhages, is sufficient to result in an interference of greater or less degree with the association tracts and projection pathways. Should a mild and generalized gliosis be present, the importance of its effect on nerve cell and fiber function might well be questioned. The problem of general gliosis is far from settled by our observations, dealing as we are with

short survival periods in the majority of cases. To settle this point further study must be made in selected cases of persons who have survived injury for several years.

SUMMARY AND CONCLUSIONS

In this contribution we have been concerned with the changes in classic neuroglia as the result of injury to the human brain. In the first few days following trauma, the astrocytes in the immediately adjacent area undergo regressive change with the formation of ameboid glia. In the zone nearest the point of injury the cells undergo complete destruction. Beyond this zone of destruction active proliferation takes place. Here, within a few hours after injury, double nucleated forms indicate active direct cell division. In a rather narrow intervening zone, apolar, bipolar and unipolar forms have been found, which, because of their ready impregnation with gold sublimate, are probably viable cells. This is furthermore suggested by the presence in these cells of double nuclei having normal morphologic characteristics. We have interpreted these elements as regressive forms capable of reversible reaction.

Gliosis occurs only as a result of tissue destruction. The degenerating tissue probably serves as a chemical stimulant to the regional astrocytes. In the formation of the glial scar, glia cells assume their active or kinetic function of space compensation in the process of healing. Extensively damaged brain tissue, which requires a rather prolonged activity on the part of the phagocytic mesoglia, delays for a considerable period the formation of the ultimate glial scar. The astrocytes taking part in this delayed reaction are themselves often victims of regressive change, particularly of a hyaline nature.

Judging from studies on comparatively recent cases, it seems likely that the neuroglial reaction is a purely local affair and consequently that generalized gliosis following head injury does not occur. The remote clinical sequelae of such injuries are largely to be interpreted on the basis of focal and distant cortical injuries. In addition, there are numerous interruptions in the connecting pathways incident to focal and subcortical injury, together with the changes following widespread petechial hemorrhages. In this sense localized gliosis is only a histologic manifestation of the damage which produces the symptoms. The changes in the nerve cells and fibers responsible for these symptoms will be considered in a future contribution.

SMALL FOCI OF DEMYELINIZATION IN THE CORTEX AND SPINAL CORD IN DIFFUSE SCLEROSIS

THEIR SIMILARITY TO THOSE OF DISSEMINATED SCLEROSIS AND DEMENTIA PARALYTICA

FREDERIC WERTHAM, M.D.
Fellow National Research Council
NEW YORK

An attempt is often made to characterize neuropathologic conditions by describing the changes of only one component of the tissue of the central nervous system. Nissl himself was forced to give up the search for specific changes of the nerve cells in different pathologic states, such as intoxications; but even today this search for specific alterations of the ganglion cells continues and claims of their existence are made. In the same way, descriptions of other individual components of the central nervous system tissue have been offered as adequate histopathologic characterization of a pathologic process and as a basis for neurologic distinctions. It is frequently overlooked that each component of the nerve tissue can react only in a limited number of ways, and that in consequence the same reactions may occur in very different conditions in response to very different causes. What is necessary for the delimitation of a histopathologic process is an analysis of the changes of each component of the tissue, of the mutual relationship of these tissue components to one another and of the topographic distribution of the pathologic changes. From this point of view an analysis of the histologic appearances in two cases will be presented. It opens up vistas for the demonstration of certain similarities between the histopathologic pictures of three neuropathologic conditions, namely, diffuse sclerosis, disseminated sclerosis and dementia paralytica.

REPORT OF CASES

CASE 1.—*Clinical History.*—A woman, aged 53, the wife of a peasant, was observed in the Schwabing Hospital.* The occurrence of neuropsychiatric conditions in the family was denied by the husband. The patient had four healthy children, their ages ranging from 16 to 24. Eight years before admission to the

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*Professor Oberndorfer, director of the pathological department of the Schwabing Hospital, made possible a histopathologic examination in this case.

hospital, she had a "kind of stroke" which affected chiefly the right side. She was in bed for four weeks. A weakness of the right side remained. A year later she had a second attack. Nocturnal enuresis was said by the husband to have existed since the beginning of the disease. The patient had many convulsive attacks, occurring several times a day. Apparently they were lighter at first, and then became more severe. She would begin to tremble, talk peculiarly, strike out with her arms and fall, often injuring herself. She also had attacks during which she drew together, became stiff, rolled her eyes, did not talk and finally fell down. Sometimes in attacks the muscles of the right side of the face were contracted. She also was subject to fuguelike states during which she ran away and could not be found. She did not return to her habitual mental condition until some hours after the attacks. She became unsteady and tremulous, and even between attacks she was very excitable. She was admitted to the hospital in a semicomatose condition. She did not react except for a slight movement of the eyelids when addressed in a raised voice.

Examination.—The positive observations were as follows: There was a cleft palate. The right upper arm and shoulder showed evidence of a recent injury. The left pupil was irregular and larger than the right; both reacted to light, the left one more than the right. There was no papilledema. When the head was turned to the side, the patient would open her eyes, wider if the head was turned to the right. The resistance was also stronger on the right than on the left side. The arms were flexed at the elbow to a right angle; they were markedly spastic and offered resistance to flexion and extension, more so on the right than on the left. The right hand and arm showed occasional spontaneous twitchings which also occurred in the lower facial area, especially on the right. During examination of the pupils, the patient raised the right arm jerkily, while the left remained at rest. The knee and ankle jerks were increased, but no definite spastic phenomena were noted. The legs were kept rotated inward, so that the feet crossed each other, a position to which the patient would always return. The tonus of the musculature of the right leg was more marked than that of the left. Wassermann tests of the blood and spinal fluid gave negative results.

Course.—During the four days of her stay in the hospital, the patient did not rouse from the deep somnolent state. The spontaneous twitchings decreased, and finally ceased. The spastic condition of the arms became somewhat less marked. The left pupil appeared wider, and finally did not react to light. The blinking reflex was demonstrable until a short time before death.

Necropsy.—General examination indicated confluent purulent bronchopneumonia, beginning pleuritis fibrinosa, granular atrophy of the kidney and struma with hemorrhages.

Macroscopic Observations in the Central Nervous System and Extent of the Lesions as Determined Microscopically: The gyri of the occipital and parietal lobes appeared somewhat atrophic. Otherwise nothing unusual was noticed on the surface of the brain. The vessels at the base showed some arteriosclerotic deposits. In frontal sections it was seen that the ventricles were enlarged. At the level of the posterior end of the thalamus on the left side there were sharply beginning atrophy and gray discoloration of the central white substance in the parietal lobe, along the upper margin of the pallium and the diagonally opposite gyri at the parietotemporal border. This atrophy and gray discoloration continued backward toward the occipital pole and forward toward the temporal pole, being easily recognizable from the hue of the white matter and the width of the cortex as compared with the width of the white matter. The iron reaction of Spatz was negative.

The thalamus appeared atrophic. The extent of the lesion was determined from frontal sections. They were stained partly by the method of Kulschitzky-Wolter and partly by those of Spielmeyer, Holzer, Nissl and Herxheimer. Smaller pieces were impregnated with silver according to the method of Bielschowsky and a modified method of Cajal. In general it can be stated that the greatest extent of the focus was found at the border between the parietal and occipital lobes. It extended forward into the temporal lobe almost to the temporal pole. The farthest end of the focus was in the gyrus temporalis superior at the border between cortex and white matter, but extending into the cortex. Another arm of the lesion, which also involved the pulvinar thalami, reached into the cortex of the insula. It became smaller, until finally only the capsula externa and the myelinated fibers of the insular cortex were affected. On the right side was a lesion that had the same appearance and that was more or less symmetrical with the lesion on the left. Its extent, however, was much smaller. At the border between the parietal and occipital lobes, the lesion was strictly limited to the

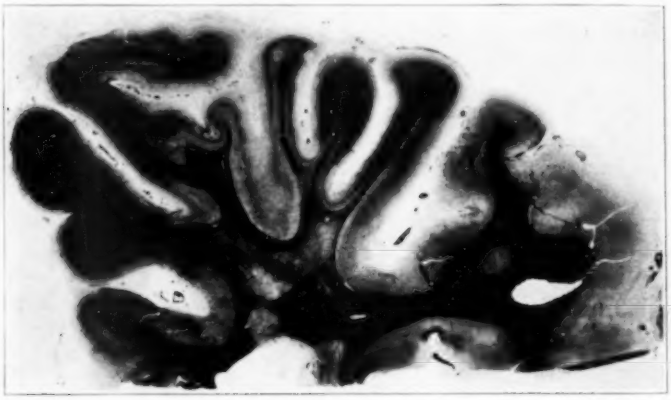

Fig. 1.—Frontal section (parieto-occipital border). Extensive diffuse demyelinization. Two small cortical foci in one occipital gyrus near the middle of the convexity. Kulschitsky-Wolter preparation.

central white substance and did not involve the intragyral myelin fibers. Only in the right temporal lobe was the extent of the lesion practically the same as on the left, with the qualification that the white matter was not so severely affected.

A frontal section (fig. 1) through the left hemisphere, approximately corresponding to the border between the occipital and parietal hemispheres, showed that the myelin fibers of the corpus callosum were well preserved here only in the upper part. The part adjacent to the ventricle was strongly affected for a considerable distance, with the result that in the myelin sheath picture this area appeared very light. This lesion ended abruptly, and there was a sharply defined border between the lesion and the myelin fibers of the hemispheres. Above the gyrus hippocampus and also adjacent to the ventricle the lesion was pronounced. The fibers of the occipital region, including the stratum sagittale externum, were also much involved. The lesion usually came to a gradual end where the intragyral portion of the white matter began. The U-fibers of Meynert were for the most part fairly well preserved in comparison with the extensive involvement of the gray matter below these structures. There were, however, definite places in

which they also were affected. In one occipital gyrus near the middle of the convexity there were two smaller foci in the cortex. The radial fibers of the cortex were also involved, especially in the deeper layers. The condition did not affect individual gyri, but spread over several gyri indiscriminately.

Another frontal section made nearer the occipital pole on the same side showed the same picture, but in a more pronounced form. Here also the myelin sheaths in the central white matter had almost completely disappeared, with the exception of the U-fibers, which were on the whole better preserved. The stratum sagittale externum was practically no longer seen. In contrast to this, the intragyral portion of the white matter seemed on the whole to be well preserved. However, in one gyrus adjacent to the fissura calcarina the myelin sheaths were markedly decimated, and there were two larger foci extending into the cortex. In only one gyrus at the upper margin of the pallium had the myelin sheaths of the intra-

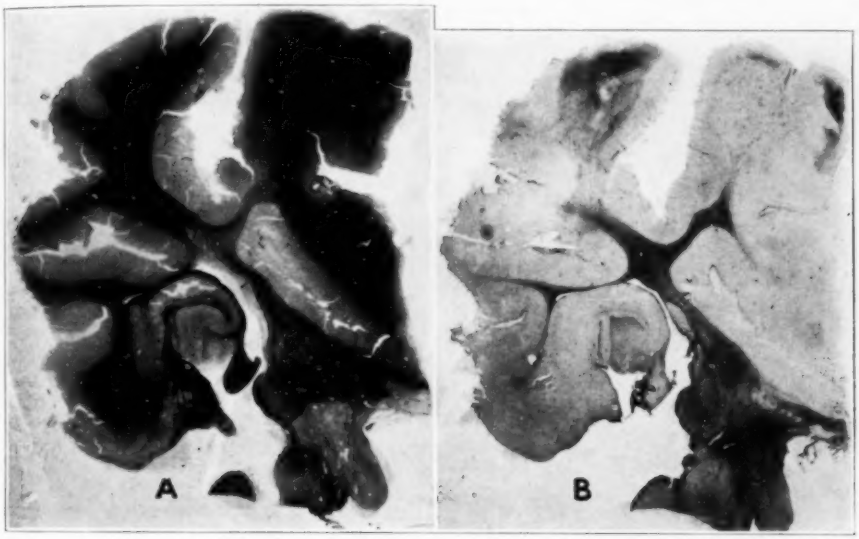

Fig. 2.—Section through the temporal lobe. Note involvement of the posterior part of the thalamus. Myelin sheath stain (*A*) and Holzer fiber stain (*B*).

gyral portion of the white matter also completely disappeared. In this section, as in the previous one, the foci extended in several places into the myelin sheath radiations of the cortex.

It is especially striking that the U-fibers were found intact in places where the myelin sheaths of the cortex were destroyed. Thus it came about that in one place nothing remained of the whole white matter except a narrow stripe of U-fibers that stood out distinctly, although the myelin sheaths of the cortex, including the Gennari stripe, had almost completely disappeared.

In the left temporal lobe the changes were much less pronounced and were much more limited in extent than in the sections previously described (parietal and occipital lobes). Here also one found the most marked change near the ventricle (inferior horn of the lateral ventricle). Then the lesion broadened into the white matter of the temporal lobe and was most marked in the first and second temporal gyri. In this section also the lesion stopped abruptly. In the

involved parts the myelin sheaths of the cortex were strongly affected. Special attention should be drawn to the participation of the thalamus. In the pulvinar the myelin sheaths were diffusely destroyed, and in the corpus geniculatum laterale they were diffusely decimated (fig. 2).

In a frontal section that passed through the substantia nigra and the nucleus ruber and also included the pulvinar, there was seen in the pulvinar and in the adjoining parts of the white matter of the insular cortex a focus that laterally was sharply defined against the cortical portion of the myelin sheaths, which were in part well preserved. As it passed downward, however, the focus diminished gradually. In the same section there was another part of the focus that progressed downward into the temporal lobe.

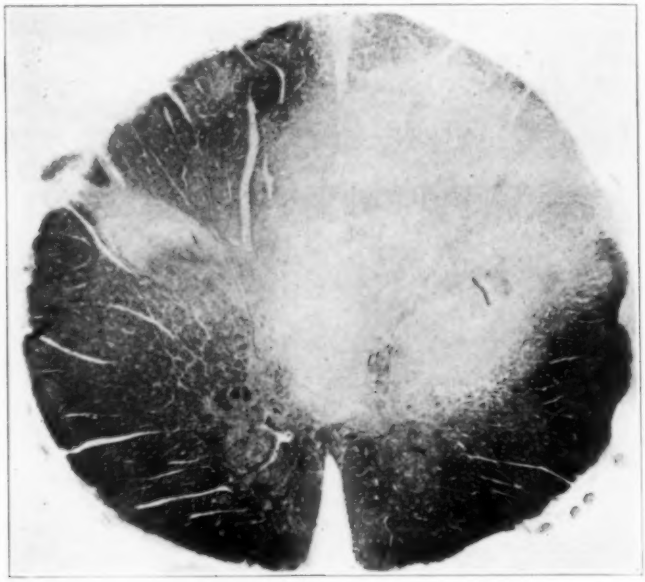

Fig. 3.—Focus of demyelinization in cervical part of the spinal cord in diffuse sclerosis. Myelin sheath preparation.

In the midbrain, pons and medulla no characteristic changes were found. In the cerebellum, numerous Purkinje cells with two nuclei were observed, an observation that in view of the uncertainty of their significance will not be especially stressed. The white matter of the cerebellum showed an increase of glia with the Nissl stain. No changes were found in the basal ganglia or in the anterior part of the thalamus. No small foci were found in the opticus, which was, however, not examined along its whole length.

In the cervical part of the cord (other parts of the cord were not available) an especially interesting condition was noted. There was a focal area of demyelinization which spread irregularly over almost half of the cross-section of the cord. In myelin sheath preparations (fig. 3) it appeared as a light area which reached on one side to the anterior horn, then—involving part of the posterior horn—spread to the periphery. It destroyed the posterior columns of one side almost completely, but also reached across the midline and involved the posterior columns of the other

side. Within the lesion not all parts were equally affected. In the periphery the original arrangement of the myelin sheaths was still preserved, although this area was markedly paled. Remnants of the myelin sheaths of the posterior horn could also be seen in the lesion itself.

Small Foci in the Cortex: There were many small areas of demyelinization diffusely distributed over the cortex, which were visible to the naked eye in stained preparations. Most of them were round and a little larger than the head of a pin (figs. 1 and 7 *A*). Some were considerably larger. It could be seen microscopically that within these areas the myelin sheaths had degenerated. As a rule the areas were clearly delimited. They usually lay in the cortex, but sometimes reached into the subcortical white matter.

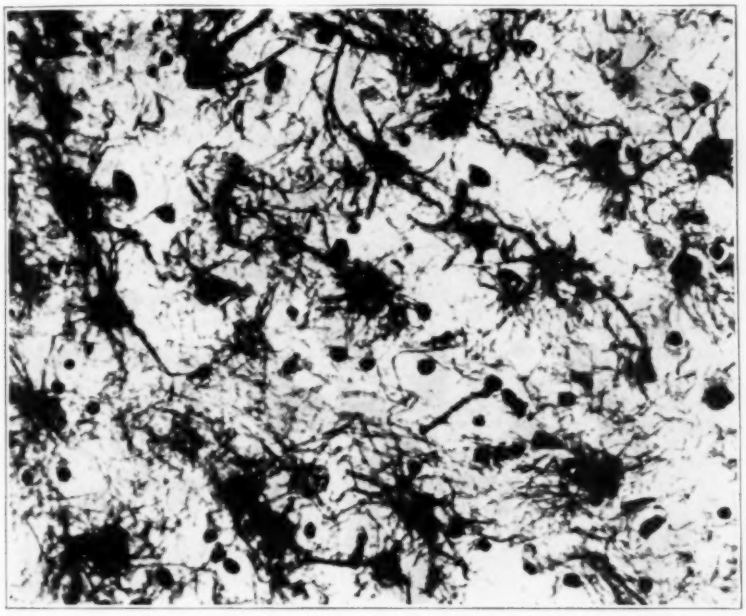

Fig. 4.—Large fibroblastic astrocytes in the thalamus. Holzer glia fiber preparation.

Histologic Details.—Myelin Sheath Stain: In the myelin sheath picture it was seen that the cerebral lesions showed rarefactions in which, however, only rarely had all the myelin sheaths completely disappeared. This complete disappearance of the myelin sheaths was observed only in a few places in the occipital lobe. Usually some relatively well preserved fibers were left. Pathologic changes of the myelin sheaths, such as tumefactions and swellings, were common.

Holzer Glia Fiber Stain: The myelin sheath picture may be considered as the negative of the glia fiber preparation, which is the positive. For wherever lesions were found in the myelin sheath stain, the Holzer glia fiber preparation showed an enormous fibrous gliosis, which kept more or less within the border of the lesion. A wealth of fibrous astrocytes was seen (fig. 4) in the pulvinar and in the corpora geniculata laterale and mediale, as well as in all those places where the lesions extended into the cortex.

Herxheimer Fat Stain: Three types of pictures were observed. First, there were areas in which lipoids were found only in the adventitial spaces and there only in small quantities. This was the case in practically all the lesions described. Secondly, there were two areas in which a great deal of fat was found. Over a considerable area in the parietal lobe, directly under the cortex and near the border of the lesion, there was evidence of fresh Abbau. Fat occurred here in compound granular corpuscles which were evidently of glial origin. The adventitial sheaths of vessels in the immediate vicinity of this place also contained many scavenger cells laden with fat. Similar evidence of recent fat Abbau occurred in the cord. Thirdly, this type of fat picture occurred only in the thalamus, where there was much lipoid material in the glia cells. The lipoid did not stain bright red, as did the scavenger cells in the vessel sheaths. Much lipoid pigment also occurred in the ganglion cells in the thalamus.

Nissl Stain: A gliosis within the lesions was apparent here also. One observed further that the larger vessels within the lesion showed considerable lymphocytic infiltration. There was also a very slight infiltration of the meninges. In the cortex definite changes could be seen. The first layer often seemed broader and richer in glia than is usual, and the glia cells there often contained pigment (lipofuscin). In the regions where the lesions were most extensive, especially in the occipital lobe, the cortex showed an increase in glia. There were many small areas where the ganglion cells had disappeared.

In the posterior part of the thalamus and in the pulvinar (included in the lesion) the number of ganglion cells had greatly decreased. The remaining cells contained much pigment. In the anterior parts of the thalamus there were no focal changes, but here also the number of nerve cells had decreased over diffuse areas.

In the central region the deeper layers of the cortex were considerably involved. Here too the number of nerve cells was reduced. The cell bodies were rounded and pale and stained homogeneously. The nuclei were dark and were usually situated at the periphery of the cell. This picture of acute swelling was very evident in the Betz cells. They appeared swollen and pale; the nuclei were at the periphery of the cell bodies, and the processes were seen for a longer distance than usual. The glial satellites sometimes showed mitotic forms. In the upper layers of the cortex the acute swelling was less definite. Cells had dropped out there, too, but to a smaller extent.

Bielschowsky and Cajal Stains: The impregnation of nerve fibers according to Bielschowsky and Cajal showed a certain agreement with the myelin sheath stain as to the condition of the nerve fibers. Where the process was most intense, scarcely any nerve fibers were left. Where the process decreased, near the margin of the lesions, more and more axis cylinders were found. The fibers that remained were altered. Sometimes they were swollen and twisted like corkscrews; sometimes they showed only tumefactions and local swellings or ball-like terminations. In the region of the cornu ammonis were small patches, somewhat like fine threadlike conglomerations, which were well impregnated with silver. In some places these were numerous. They also occurred in the fascia dentata. They were senile plaques resembling the so-called feltwork (Filzwerke).

Histologic Details of the Lesion in the Cord.—In the mesial parts of the lesion the fat stain showed relatively little fat; it was contained in glia cells that did not form compound granular bodies. Near the margin of the focus there was much more fat, and here it occurred in scavenger cells as well as in fixed glia cells. The vessel sheaths in the center of the lesion and at the periphery contained a considerable amount of lipoid material in scavenger cells.

The glia fiber preparation (Holzer stain) showed a dense fibrous gliosis approximately corresponding to the limits of the lesion, as indicated by the myelin sheath stain. Sections stained with cresyl violet showed a marked proliferation of glia, mainly protoplasmic glia, around the whole margin of the lesion. The anterior horn cells were well preserved and did not seem to be reduced in number. The cells of both posterior horns (one of which was included in the lesion) also seemed normal. In other segments of the cord a diffuse fibrous gliosis was observed over the whole cross-section, most pronounced at the junction of the white and the gray matter.

The axis cylinders, according to the Bielschowsky preparations, were much less involved than the myelin sheaths. In the posterior horn, tumefactions and swellings of the nerve fibers could be seen, but these changes were not pronounced.

COMMENT

While most of the observations reported speak for themselves, some need a discussion of their interpretation and significance. The changes in the posterior part of the thalamus, especially in the pulvinar and the mesial and lateral geniculate bodies, were a primary effect of the pathologic process. This is evident from the fact that the pathologic changes were not restricted to these structures, but indiscriminately affected the adjacent parts as well. If, for example, the changes in the pulvinar had been secondary and due to involvement of the optic radiation, which it is true was very great, the changes described would have been restricted to the pulvinar and would not in the same manner and intensity have affected the other parts of this whole region.

The absence of fat within the lesion indicates that in the main the lesion was the effect of a chronic process. This tallies with the clinical history, according to which the disease lasted eight years. In only two places was fresh Abbau of lipoid material found. In these places, therefore, the pathologic process was not ended. One of these more recent lesions was the focus in the cord; the other was near the margin of the main lesion in the brain, namely, in the left parietal lobe. From the latter area important conclusions as to the topographic progress of the lesion can be drawn. In those parts lying near the center of the lesion, no fat Abbau was found. As one approached the margin of the lesion, where there was fresh fat Abbau, a small region was first encountered where lipoid material was present only in the vessel sheaths and not in the nerve tissue. Finally, as the region was reached where the effects of the pathologic process were more recent and apparently still continuing, fat was found in numerous compound granular corpuscles in the nerve tissue and in the perivascular spaces. This distribution would indicate that the pathologic process progressed from inside outward, as has also been suggested by Gans and by Bielschowsky.

The lymphocytic infiltrations of the blood vessels probably denote not a truly inflammatory phenomenon, but a secondary reaction. One

may conclude this from the fact that perivascular infiltrations were found in the larger vessels only, and from the disproportion between the main changes and the inflammatory phenomena.

The relationship between the histologic pictures presented by the fat stain and by the glia fiber stain of the lesion of the cord is of special significance. The fat stain showed a fair amount of lipoid material, evidence that Abbau phenomena were still continuing. The process, therefore, could not be a very old one in this region. The Holzer preparation showed an enormous fibrous gliosis in the same area. This would indicate that a strong proliferation of fibrous glia may occur early, e. g., even in the acute or subacute stage.

The most conspicuous manifestations in this case were: an extensive and intense continuous demyelinization, with less pronounced involvement of the axis cylinders, mainly in the white matter of the occipital, parietal and temporal lobes; an enormous fibrous gliosis corresponding to the demyelinated areas; more or less symmetrical distribution on both sides, and chronicity of the process—although in two small places there was evidence of subacute stages. From these characteristics one may include this case in the large group of those of diffuse sclerosis.[1] Since under this term heterogeneous groups are subsumed, one may make the diagnosis of diffuse sclerosis more specific by the statement that the condition occurred in an adult, ran a chronic course, and was more of the degenerative than of the acute infectious variety.

Two features of the case need especial emphasis. One is the involvement of the gray matter. In the pulvinar and the lateral and medial geniculate bodies there was diffuse demyelinization not explainable as retrograde or secondary degeneration (fig. 2). The nerve cells were also affected, and there was proliferation of fibroblastic astrocytes with marked fibrous gliosis (fig. 4). The cortex was also involved. In the literature on diffuse sclerosis the statement can frequently be found that the process comes to a halt at the U-fibers, and that therefore the

1. The large literature on diffuse sclerosis can be found in the following recent publications: Gasul, M.: Schilder's disease (Encephalitis periaxialis diffusa), Am. J. Dis. Child. **39**:595 (March) 1930. Gagel, O.: Zur Frage der diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:418, 1927. Jakob: Die "diffüse Sklerose" des Grosshirnmarkes spezielle Histopathologie des Grosshirns, Vienna, Franz Deuticke, 1929. Globus, J. J., and Strauss, Israel: Progressive Degenerative Subcortical Encephalopathy (Schilder's disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffüse Sklerose, (Leukodystrophia cerebri progressiva hereditaria), J. f. Psychol. u. Neurol. **36**:131, 1928. Stewart, T.; Greenfield, J. G., and Blandy, M. A.: Encephalitis Periaxialis Diffusa, Brain **50**:1, 1927. Bielschowsky, F.: Die Bedeutung des Infektes für die diffüse Sklerose, zugleich ein Beitrag zur Klinik und Pathologie der diffüsen Sklerose, J. f. Psychol. u. Neurol. **33**:12, 1927.

cortex is not involved. It was clearly demonstrated in this case, however, that although the U-fibers may remain intact, a study of the myeloarchictectonics of the cortex above these U-fibers may show a very severe involvement of the myelin sheaths in the cortex.

In the myelin sheath preparations, three types of involvement of the myelin sheaths of the cortex could be distinguished. First, there are places where the U-fibers were destroyed and the lesions reached into the cortex. Second, the cortex was severely affected in places where the U-fibers were still intact. Third, small patches of demyelinization could be found which were sharply defined and lay either entirely in the cortex or partly in the subcortical white matter and partly in the cortex.

In Nissl stains of the cortex there were diffusely distributed areas where ganglion cells had been destroyed. The acute swelling found especially in the Betz cells, but also to some extent in other ganglion cells, cannot be regarded as belonging directly to the manifestations of the main pathologic process. Does this involvement of the gray matter take the case out of the group of diffuse sclerosis? I believe that too much emphasis has been put on a schematic contrast between involvement of the white and of the gray matter. One has attempted, for example, to use this contrast for a differentiation of the blastomatous forms of diffuse sclerosis, e. g., of gliomas of the central white matter of the hemispheres and of infectious degenerative forms. It seems, however, that in gliomas the gray matter may be spared, while in diffuse sclerosis involvement of the gray matter frequently occurs. Especially incorrect is the statement that the intactness of the U-fibers is an indication of the intactness of the cortex. Involvement of the striatum, thalamus and geniculate bodies is mentioned in a number of reports of cases of diffuse sclerosis—changes in the gray matter that cannot be entirely due to retrograde and secondary degeneration. With reference to the changes in the thalamus in one of his cases Bielschowsky stated this expressly, saying that without doubt along with the fibers of the white matter many ganglion cells are directly destroyed. In an early case of diffuse sclerosis Bodechtel and Gutmann [2] described encephalitic changes involving gray and white matter. On the whole, finer changes in the gray matter, as seen in the Nissl picture—for example, the occurence of acellular areas—do not seem to have been sufficiently investigated in fully developed cases. The involvement of the gray matter in the case discussed here, therefore, would not rule out the diagnosis of diffuse sclerosis.

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2. Bodechtel, G., and Gutmann, E.: Diffuse Encephalitis mit sklerosierender Entzündung des Hemisphärenmarkes, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**: 601, 1931.

The occurrence in the cord and in the cortex of small areas of demyelinization, which in themselves cannot be distinguished from plaques of multiple sclerosis, might present greater diagnostic difficulties. The problem of the differential diagnosis between multiple sclerosis and diffuse sclerosis therefore presents itself. It would seem to me that one may speak of the present case as one of diffuse sclerosis for the following reasons: Such large continuous lesions as the one found here, involving a good part of the central white matter of several lobes, are not usually observed in disseminated sclerosis. (The case of Gans [3] is so far an exceptional observation. In this case there was a diffuse continuous bilateral sclerotic lesion reaching from the frontal to the occipital pole.) On the other hand, small lesions not distinguishable from those of disseminated sclerosis have been seen in a number of cases of diffuse sclerosis. They have been reported as occurring in various locations, as in the opticus, pons, medulla oblongata and hemispheres (Hallervorden). The possible occurrence of such lesions in the spinal cord has been neglected. Hallervorden discussed small lesions, but did not mention that they may occur in the cord. According to Jakob, the cord usually shows only evidence of secondary degeneration. Beneke also regarded very large foci of sclerosis in the cord in his case as due to secondary degeneration. Bielschowsky mentioned in the report of his first case (in the second case the cord was not available) that the possibility of the existence of a primary patch of demyelinization in the cord could not be ruled out. There was a bilateral area of secondary degeneration in his case, sharply delimited to the area of the lateral pyramidal tract. In this area of demyelinization the number of persisting myelinated fibers was, however, much smaller than one is wont to find in secondary degeneration (overlap of rubrospinal tracts and existence of short neurons). Bielschowsky considered the interesting possibility that a descending degeneration covered up a primary process of demyelinization in the cord. The occurrence of small areas of demyelinization in the cortex, such as was demonstrated in my two cases, is regarded as so characteristic of multiple sclerosis that Hallervorden considered their absence in diffuse sclerosis as a differential diagnostic sign. Gagel considered the absence of small focal areas of demyelinization in the spinal cord and cortex as so characteristic of diffuse sclerosis that he regarded them as one of the differential diagnostic signs between diffuse sclerosis and Pelizaeus-Merzbacher disease, in which one finds such lesions.

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3. Gans, A.: De Uitbreiding der Ziekelijke Veranderingen bij een Geval van Sclérose en Plaques met diffuse Hersensclerose als Bewijs voor het Naar Buiten Treden der Sghadelijkheid door den Wand der Ventrikels, Nederl. tijdschr. v. geenesk. **69**:533, 1925.

In summary, one may say that circumscribed lesions in the cord in diffuse sclerosis have received inadequate attention. Involvement of the cord has been regarded either as evidence of secondary degeneration or as a pathognomonic sign that the case was one of multiple and not of diffuse sclerosis. It seems important that, as in the case reported here, small focal areas of demyelinization may occur in diffuse sclerosis in the cord, far away from the large area of demyelinization in the cerebral lobes.

Such small foci of demyelinization in the cortex as those seen in this case have not been mentioned in the large literature on diffuse sclerosis. They are described here for the first time.

It seems that these small areas of demyelinization do not rule out the diagnosis of diffuse sclerosis, but that they may be considered as a new feature of this condition.

Since case 2 presents many histopathologic similarities to case 1, it will be presented more briefly.

CASE 2.*—*Clinical History.*—From the available data it was not possible to determine the exact date of onset of the disease. The condition lasted at least from eleven to twelve years. The patient was first admitted to the hospital at the age of 30. One brother was said to have suffered from a nervous disorder. The patient learned moderately well in school. After the World War, tremor of the extremities, especially of the right arm and leg, developed. He had to give up work as a laborer in a factory. He became very excitable. The tremor in the arms and legs was easily provoked when he became in any way emotionally stirred. He had occasional headaches, more frequently on the right side, and vision was at times blurred. About one or two years before admission, he began to sleep a great deal. He would also fall asleep during the day while sitting at a table or in the theater if he leaned against a pillar. This readiness to fall asleep during the day was also noticed in the hospital, and gave rise to the diagnostic impression of a postencephalitic condition.

Examination.—The pupils were moderately large and did not react to light; they responded very little in accommodation. The left arm was atrophic, owing to a trauma suffered when the patient was a child. The tendon reflexes were stronger on the right than on the left. There was no Babinski sign and no clonus. The abdominal reflexes were absent. Intention tremor was noticed in both hands. In the Romberg position a marked tremor of the right arm was noticed. The patient walked with a cane, but was able to walk without it. He complained of pains in the muscles on pressure, and also when putting on his trousers. Speech was scanning, and during conversation became very much disturbed and indistinct. The Wassermann reaction of the spinal fluid was negative; the mastic curve was normal. There were 8 cells per cubic millimeter of fluid. In the hospital there was once incontinence of urine. A diagnosis of multiple sclerosis was made.

Course.—The patient was readmitted to the hospital several times, once after having fallen on the street. Once, between admissions to the hospital, he mis-

* Dr. Neubürger, prosector of the Deutsche Forschungsanstalt für Psychiatrie, provided opportunity for investigating this case.

appropriated funds, for which he was sentenced to four weeks in jail. At that time he wanted the physicians to declare him not responsible on account of his nervous condition. He drank a great deal, was observed to approach women and girls on the street, showed a tendency to make homosexual advances, was arrested for begging, and seems to have drifted into a kind of behavior that necessitated admission to a state hospital. There he had a tendency to silly pranks. At times he was very irritable, and had states of great excitement. In view of the fact that he sought compensation for war service a large part of his behavior was ascribed to simulation. Five years before death, epileptiform attacks appeared. They began in the left side of the face, and then spread to the right arm and leg. They lasted from three to four minutes. The patient died at the age of 37 after a series of epileptiform attacks.

Autopsy.—There was hypostatic pneumonia. There were endocardial hemorrhages in the left ventricle and hemorrhages in the pleura of both lungs and in the mucous membranes of the stomach and duodenum.

Macroscopic Observations of the Central Nervous System: The surface of the brain appeared normal. In frontal sections through the right hemisphere a gray discoloration of the white matter was seen in the section corresponding to the border of the occipital and parietal lobes. This discoloration was most pronounced near the posterior horn of the ventricle. It reached from there in all directions, especially into the basal parts of the occipital lobe. The gray hue was not uniform, being more intense in the center of the lesion and merging with the normal color of the white matter toward the outside edges.

In sections passing through the more anterior parts of the brain the extent of the lesion could not be recognized so well. It became smaller and seemed to be restricted to the more central parts. A slight gray discoloration could still be seen near the inferior horn of the lateral ventricle in the temporal lobe. From the region of the ventricle some branches reached toward the cortex. At the place where the anterior end of the thalamus begins, sections still showed slight discoloration of the white matter.

The changes in the left hemisphere resembled those in the right, and so far as could be determined macroscopically they had the same extent.

Microscopic Observations: Various parts of the brain were examined microscopically with the aid of the usual survey and analytic methods. On account of the possibility of the occurrence of small foci, special attention was given to the cerebellum, pons, medulla and spinal cord, as well as to the cerebral cortex. The opticus was not available.

In the myelin sheath picture the cerebral lesion showed characteristics similar to those of case 1. At the border of the parietal and occipital lobes, for example, the demyelinization was most pronounced at the center of the lesion, in the vicinity of the posterior horn of the ventricle (fig. 5). From there it spread in all directions. It decreased in intensity both diffusely and locally. The staining propensity of the white matter as a whole was decreased in places, so that the whole central white matter of a given area appeared light, or there were lighter-stained patches in regions where the myelin sheaths were generally well preserved. In comparison with case 1, the demyelinization did not reach so far into the intragyral portion of the white matter of the individual gyri. The U-fibers were for the most part well preserved, so that they stood out against the demyelinated regions. However, in a number of places the U-fibers also were involved. In one preparation, for instance, there were four places in which both the U-fibers and the cortex above them were very much involved. In one region this was especially conspicuous because the Gennari stripe as well as the radiary fibers was destroyed,

so that the whole cortex appeared almost completely demyelinated. In one gyrus there was in the cortex a small focus about the size of a pinhead, similar to those described in case 1. In this case, however, there was not complete demyelinization, but only a paling, which was visible to the naked eye.

In the frontal lobe the continuation of the lesion appeared again most pronounced in the central region near the lateral ventricle (myelin sheath stain), and it reached to the fibers of the corpus callosum in the hemispheres. From the central portions to the gyri, the lesion gradually decreased.

In sections through the basal ganglia one saw a continuation of the lesion, with complete demyelinization above the putamen near the lateral ventricle. It reached a short distance into the capsula interna and the upper part of the claustrum. From there on laterally it was seen again that the white matter of the hemispheres appeared diffusely light. In the upper corner of the putamen there was a small focus. There was also in the lowest part of the section a large, round,

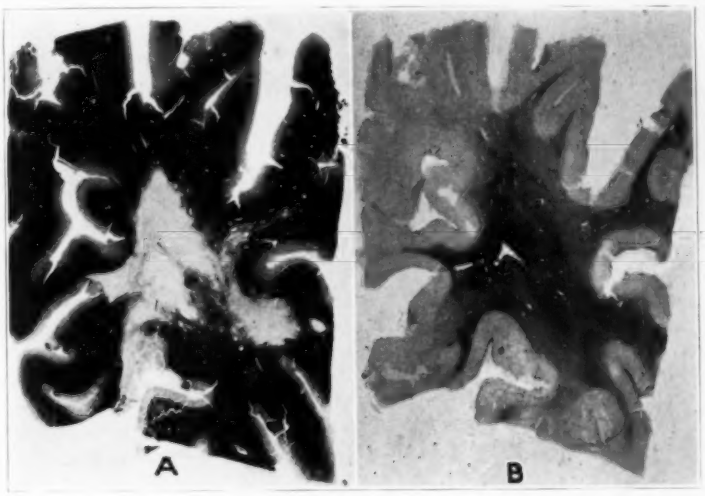

Fig. 5.—Section through occipito-parietal border. The Holzer glia fiber preparation (*B*) demonstrates the diffuse extent of the lesion better than the myelin sheath preparation (*A*).

macroscopically visible focus. The putamen, particularly in its upper parts, showed a marked status fibrosus. In the same section there was a small, also macroscopically visible focus in the anterior nucleus of the thalamus. Whether these foci in the basal ganglia were in connection with the large lesion was left undetermined. The myelin sheaths which were still visible within the lesions showed on the whole no pronounced changes.

In Herxheimer fat preparations, no signs of fat Abbau were seen. Only in one place near the parietal occipital border a few compound granular corpuscles laden with fat were seen around a vessel.

Even macroscopically, it could be seen in Holzer glia fiber stains that the gliosis extended much farther than the demyelinization indicated in the myelin sheath preparations (fig. 5). In places where demyelinization was most complete the gliosis was most intense, but it was also very pronounced in the intragyral portions

of the white matter. The white matter was filled with dense fibers, and where the process reached into the cortex fibroblastic astrocytes were found in the deeper layers of the cortex. Frontal sections showed the same kind of fibrous gliosis, and gave also the impression of a considerable overlapping of the borders of the lesion as was indicated in myelin sheath stains. The same condition was revealed by sections through the basal ganglia, where the densest gliosis occurred in the lesion above the putamen, which has been previously described.

A considerable gliosis occurred also in the whole capsula externa and in the intragyral portion of the white matter of the insula. A rather massive gliosis was found in the lesion in the thalamus. In contrast to this, the focus in the lower part of the putamen was relatively poor in fibrous glia. Here were found only perivascular glia fibers and a few large fibroblastic astrocytes near the smaller vessels and in the tissue. In the upper part of the putamen, where a status fibrosus was found, no gliosis was present.

The preparations stained according to Bielschowsky's neurofibril stain agreed with the myelin sheath stains, inasmuch as the regions with the most pronounced demyelinization also showed the most intensive destruction of the axis cylinders. But in no place was the decimation of axis cylinders as intense as that of the myelin sheaths. Finer changes of the axis cylinders were not very marked.

With the Nissl stain, characteristic changes of ganglion cells were not noted. The meninges were slightly infiltrated with lymphocytes and a few plasma cells in some places. The vessels in the subcortical white matter also showed slight infiltration with lymphocytes. The central parts of the lesions, which showed the most pronounced gliosis, looked pale with the Nissl stain. This was due to the fact that in the outer parts of the lesions the glia cells were more numerous, whereas in the central parts where the glial net was thickest there were fewer cells.

In the cerebellum there were two symmetrical lesions between the nucleus dentatus and the brachia conjunctiva ad pontem. In the central parts of these lesions there was practically complete demyelinization. The dentate nuclei were involved in the most pronounced parts of the lesion. Another lesion of the same nature occurred in the white matter of the vermis. These lesions were very probably connected. The myelin fibers that remained in the lesions showed various pathologic changes—swellings, tumefactions, etc. In several places the myelin sheaths of the cortex were involved, as they were in the cerebral cortex.

With the Holzer stain, a diffuse fibrous gliosis was shown through the whole region, of varying intensity. The Bergmann glia fibers were not increased. The pronounced gliosis in the intralobular part of the white matter was very striking, even in places where the myelin sheath stain did not allow the recognition of any pathologic changes. This was similar to observations in the cerebrum.

One lesion in the cerebellum deserves special attention on account of its histologic peculiarities. Whether or not it was in connection with other lesions in that region was not determined. Within a completely demyelinated area, small areas of intact myelin sheaths stood out, very clearly stained. In several cases it could be seen that they were around blood vessels, an observation verified in van Gieson preparations. The myelin sheaths in these intact islands seemed to run very irregularly, although mainly around the blood vessels. With Bielschowsky stains these whorls showed the same structure, with neurofibrils going in all directions.

There was little doubt that the lesions in the cerebellum were in connection with lesions in the pons and medulla. In a section through the pons, the tegmentum had a diffuse light appearance (in myelin sheath preparations), and

glia fiber stains showed considerable gliosis. In the middle of the pons there was also a small completely demyelinated area.

No fat was demonstrated in the cerebellum or pons. The nerve cells of the cerebellum showed no significant changes. There was a very slight infiltration of the blood vessels within the lesions.

The cervical part of the cord showed in myelin sheath preparations a paling in the region of the posterior columns. To this corresponded a marked fibrous gliosis. Besides this there were in the lateral parts of the posterior column two small round lesions with well defined borders, in which no myelin sheaths were stained and in which an intense fibrous gliosis occurred (fig. 6 *A*).

Comment.—The main features of this case were: large continuous symmetrical lesions with demyelinization and fibrous gliosis in the cerebral hemispheres reaching from the occipital to the frontal lobes,

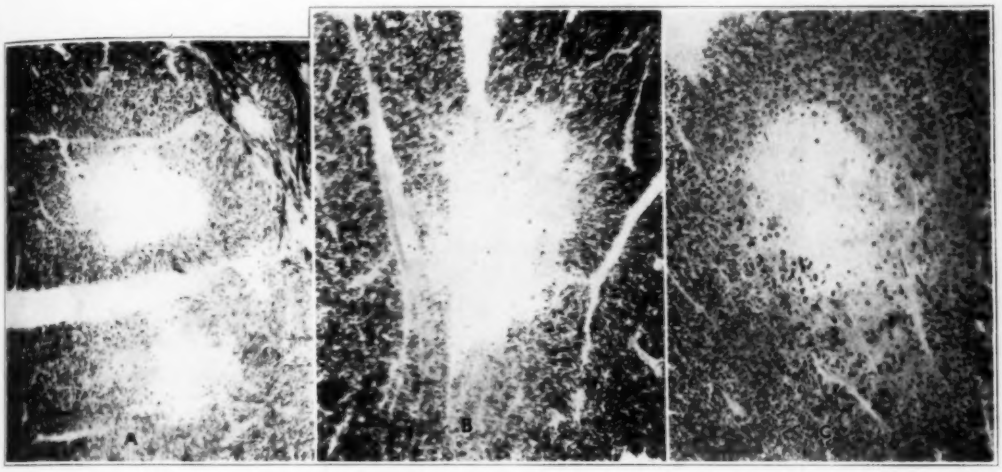

Fig. 6.—Small foci of demyelinization in the spinal cord in diffuse sclerosis (*A*), multiple sclerosis (*B*) and dementia paralytica (*C*). Myelin sheath preparations.

occasionally invading the gray matter (cortex, putamen, posterior horn); similar lesions in the cerebellum and medulla oblongata which were seemingly connected and therefore also formed a rather large lesion. Besides this, there were smaller lesions, of which the two foci in the cervical part of the cord deserve attention in connection with the present study. These small foci were far away from the large lesions and cannot be explained as due to secondary degeneration. The whole picture was a chronic, even a terminal one; there was no evidence of acute "Abbau" phenomena.

Diagnostically, the same considerations apply as in case 1. The process in the cerebrum may be subsumed under the diagnostic heading of diffuse sclerosis, of a variety with an eminently chronic course, in

an adult and of a more degenerative than infectious nature. What was said concerning the involvement of the gray matter in case 1 applies here also. It does not speak against the diagnosis of diffuse sclerosis, because while this involvement of the gray matter is usually neglected in discussions of diffuse sclerosis, it is nevertheless a feature that is mentioned in not a few of the published reports of cases. For the smaller lesions, the same considerations that were made in case 1 apply with regard to the differential diagnosis of disseminated sclerosis. The case has undoubtedly great similarity to forms of disseminated sclerosis.

The small lesions in the spinal cord in this case have to be considered, with the lesions in the cortex and cord in case 1, as a feature hitherto not demonstrated in diffuse sclerosis. One might think of a special form of diffuse sclerosis that is, as it were, complicated by such smaller lesions. Should one make such a distinction, one would have to reckon the case reported by Gans as belonging to the same group. But it is more likely that such smaller lesions are not altogether alien to diffuse sclerosis, and that they can occur in this condition, although they have so far either been overlooked or not previously demonstrated.

GENERAL COMMENT

The occurrence of such small focal areas of demyelinization in different parts of the central nervous system, involving especially the cortex but also the cord, is not restricted to diffuse sclerosis. Such lesions are also found in dementia paralytica. The diffuse destruction of myelinated fibers in dementia paralytica has, of course, long been recognized. The small focal patches of demyelinization, on the other hand, were long neglected. They received little attention and were regarded as artefacts. The first description of them was given by Borda,[4] who also drew attention to their similarity to lesions in multiple sclerosis, and later they were described by Fischer.[5] Fischer found these "spotty areas of demyelinization" in thirteen of twenty-five cases of dementia paralytica. In one case the lesions were found in the left precentral convolution in a patient who had had paralysis of the right arm. Spielmeyer[6] drew attention to the possibility of their occur-

4. Borda, I. S.: Paralysie générale progressive. Extrait de la Sociedad medica argentina, Buenos Aires, 1906; quoted by Fischer, O.: Wien. klin. Wchnschr., vol. 19, 1906.

5. Fischer, Oskar: Ueber einen eigenartigen Markfaserschwund in der Hirnrinde bei Paralyse, Wien. klin. Wchnschr., vol. 19, 1906.

6. Spielmeyer, W.: Ueber einige anatomische Ähnlichkeiten zwischen progressiven Paralyse und multipler Sklerose (Untersuchungen ueber herdförmigen Markfaserschwund bei Paralyse), Ztschr. f. d. ges. Neurol. u. Psychiat. **11**:660, 1910.

rence in the spinal cord. Later, Kufs [7] found the same lesions in the spinal cord and in the medulla oblongata. It is not necessary here to consider the nature of these focal areas of demyelinization in dementia paralytica. They have been described by Kaes, Borda, Fischer, Siemerling, Spielmeyer, Kufs, Bielschowsky, Jakob and others. A report of a case of dementia paralytica published by Riese,[8] in which focal lesions were found in the cord does not, however, belong to this group. The involvement of the cord in this case seems to have been due largely to syphilitic affection of the blood vessels.

Bielschowsky,[9] in 1919, referred these focal lesions in dementia paralytica to the "inflammatory side of the paralytic process." He found in fresh lesions a sharply delimited hyperemia of the capillaries and changes in the ground substance referable to edema and sponginess of the tissue. From these signs he regarded the local process as an inflammatory one. Jahnel [10] expressed the view that the focal demyelinization might be due to colonies of spirochetes. He has observed that such focal colonies of spirochetes do exist, besides their diffuse distribution throughout the central nervous system. But this coincidence cannot be demonstrated because the focal areas of demyelinization might develop after the spirochetes have already disappeared, quite apart from the fact that it is not possible to combine myelin sheath and spirochete stains. According to Jahnel, there is between these small focal areas of demyelinization and the large foci of the Lissauer type of dementia paralytica a difference only of degree, whereas Bielschowsky would adduce other factors also for the development of this "lobar paralytic sclerosis," namely, the status spongiosus of the cortex and the unusually severe involvement of the subcortical white matter. Steiner [11] recently expressed the view that these small foci of demyelinization in the cortex in dementia paralytica have a relationship to a special type of degeneration of the spirochetes, their extracellular degeneration. Spielmeyer has drawn attention to the striking similarity between these foci in dementia paralytica and the typical lesions of multiple sclerosis.

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7. Kufs, H.: Ueber den herdförmigen Markfaserschwund und die polysklerotischen Formen der Paralyse. Zugleich ein Beitrag zur Pathogenese der multiplen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:289, 1929.

8. Riese: Rückenmarksveränderungen eines Paralytikers. Arch. f. Psychiat. **60**:1, 1919.

9. Bielschowsky, M.: Ueber Markfleckenbildung und spongiösen Schichtenschwund in der Hirnrinde der Paralytiker, J. f. Psychol. u. Neurol. **25**:72, 1919.

10. Jahnel, F.: Ueber einige Beziehungen der Spirochäten zu dem paralytischen Krankheitsvorgang, Ztschr. f. d. ges. Neurol. u. Psychiat. **42**:21, 1918.

11. Steiner, G.: Krankheitserreger und Gewebsbefund bei progressiver Paralyse (Pathogenese des herdförmigen Markscheidenzerfalls, Allg. Ztschr. f. Psychiat. **93**:384, 1930.

Since it has been demonstrated in this study that such focal areas of demyelinization may occur in the cortex and the spinal cord in diffuse sclerosis, one may say that the same type of lesion may exist in the brain and spinal cord in multiple sclerosis, dementia paralytica and diffuse sclerosis. This similarity is striking enough to warrant an attempt to find out whether finer histologic analysis can reveal any significant differences. Spielmeyer has pointed out the great similarity between these lesions in multiple sclerosis and dementia paralytica. He stated (1929) that he knew no process except dementia paralytica in which lesions occur so similar in every respect to those of disseminated sclerosis. I have studied the nature and occurrence of these lesions in a considerable number of cases of multiple sclerosis and dementia paralytica. With the exception of their number and topographic distribution, no characteristic differences from the small foci in diffuse sclerosis were found (figs. 6 and 7). It seems, therefore, that the circle of conditions similar in some respects can be extended to include diffuse sclerosis. Apart from the occurrence of these small areas of demyelinization in the cortex and in the spinal cord, Spielmeyer called attention to two other similar features of multiple sclerosis and dementia paralytica: the plasma cell infiltration of vessels and meninges and the occurrence of diffuse demyelinization on the cortex aside from these "plaques." Both these features may also occur in diffuse sclerosis. It is interesting that there exists another similarity between diffuse sclerosis and dementia paralytica that is not usually considered, namely, the existence of diffuse sclerotic lesions in the white matter. Gianulli [12] reported a case in which there was diffuse sclerosis in the white matter and in which he could demonstrate the presence of spirochetes. He considered the case as one of diffuse sclerosis. It seems likely from the author's description, however, that this was a case of dementia paralytica. I have also had occasion to see a case of dementia paralytica [13] in which there was extensive sclerosis in the white matter, which could not be regarded as due to a process of secondary degeneration.

The main difference between the three conditions that show these small areas of demyelinization lies in the number of the lesions, their general distribution in the central nervous system, and of course their association with the other histopathologic reactions of the central nervous system in each disease.

The small lesion of the cord in the second case of diffuse sclerosis (fig. 6 *A*) resembles very closely the lesions found in subacute combined degeneration, and if one regards this focus alone it cannot be distinguished in histologic details from such lesions. This same small

12. Gianulli, F.: Ueber die Pathogenese der diffusen Hirnsklerose (Strümpell' sche Krankheit), Deutsche Ztschr. f. Nervenh. **71**:306, 1921.

13. The report of this case is being published as "Fall Raster" by Dr. Müller.

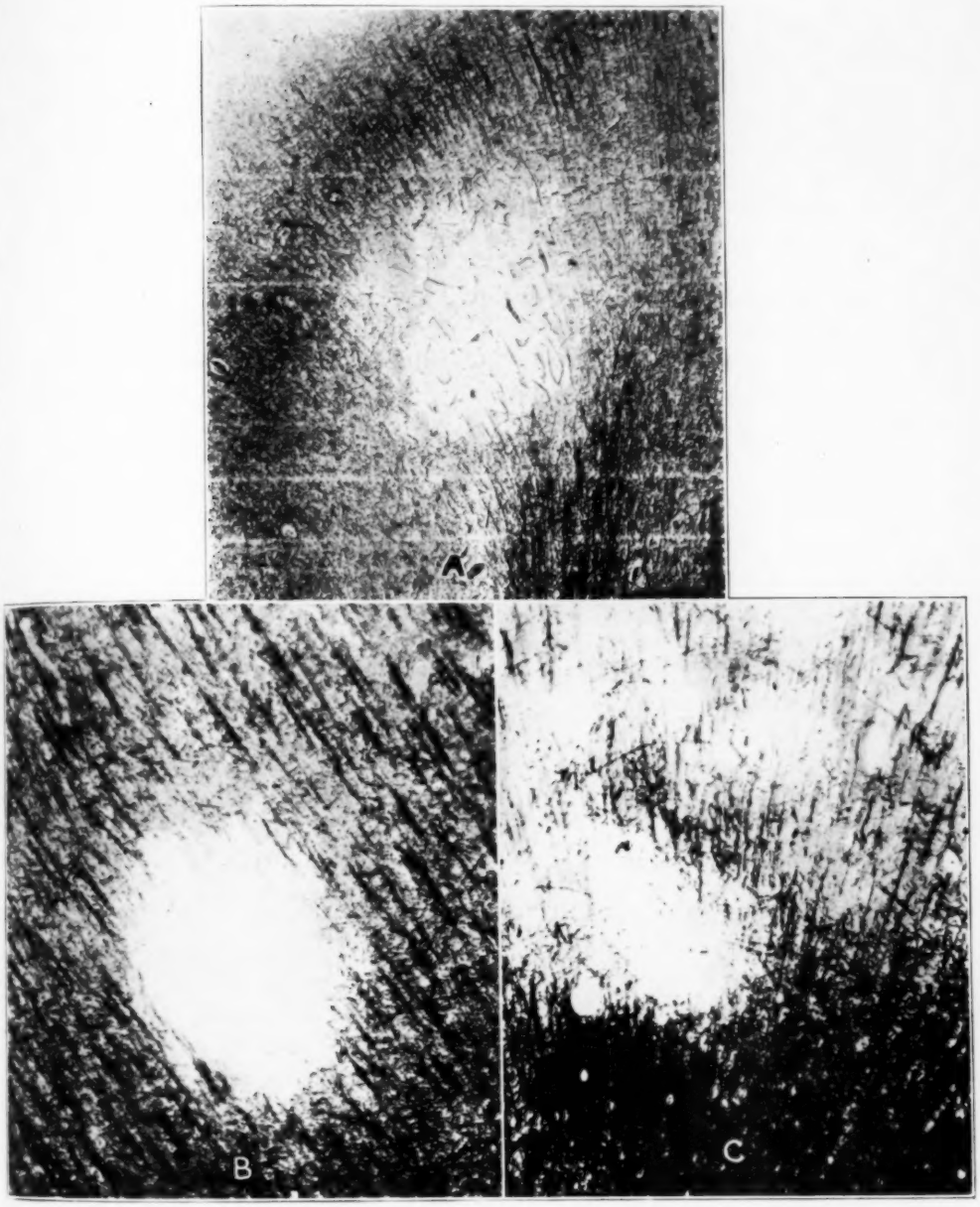

Fig. 7.—Small foci of demyelinization in the cortex in diffuse sclerosis (*A*), multiple sclerosis (*B*) and dementia paralytica (*C*). Myelin sheath preparations.

type of lesion I found also in dementia paralytica and in disseminated sclerosis. It would be necessary to study in serial sections whether such small lesions are not merely branches of larger plaques of the nature of disseminated sclerosis, or whether they have the characteristic irregular longitudinal extent of the lesions of subacute combined degeneration. The observation of such lesions in dementia paralytica seems to me to be particularly important, since in this condition a real subacute combined degeneration may occur. Homén has already pointed out that in some spinal conditions in dementia paralytica one has to think of subacute combined degeneration. Bodechtel recently observed a case in which a subacute combined degeneration with a characteristic "pseudosystematic" distribution of lesions in the tracts of the spinal cord occurred in dementia paralytica. He assumed that the severe general bodily condition of dementia paralytica may cause, in a person predisposed to it, the same type of funicular spinal disease (subacute combined degeneration) as that occurring in pernicious anemia and other conditions.

It is of considerable interest that in three diseases that present a very different appearance, in only one of which the etiology is known, practically the same type of lesion, such as these focal areas of demyelinization, may occur. Workers in histopathology have often been tempted to draw from such histopathologic similarities inferences as to etiology. It is indeed striking that such similarity in pathologic changes may occur in diseases that are otherwise so different. One may raise the question whether the similarities demonstrated here do not show certain pathogenic connections among the three diseases. But one has to distinguish between the pathogenic process, e. g., the mode in which a certain disease process develops and manifests itself histopathologically, and the cause of the disease process, the etiologic factor. It should not be forgotten that one is dealing with end-stages of pathologic anatomic changes, and that for their development other factors may be of more influence than the etiologic factor itself. The similarities could be dependent not only on the way in which the etiologic factor works itself out, but also on the reaction of the tissue proper, which is limited in its range of possible reactions by its structure and composition. The demonstration of similarities among the three diseases, therefore, may give a hint as to possible pathogenetic connections; but it does not allow etiologic conclusions based on the histopathologic observations.

SUMMARY

1. Small foci of demyelinization may occur in the spinal cord in diffuse sclerosis far from the large lesion in the cerebrum. These foci are primary and not due to secondary degeneration. In case 1 they

were similar to the plaques of disseminated sclerosis, and in case 2 they resembled the lesions in subacute combined degeneration.

2. Small areas of demyelinization in the cortex also, not previously described in this condition, are demonstrated in diffuse sclerosis.

3. These small foci of demyelinization in the spinal cord and in the cortex are of the same type as those found in disseminated sclerosis and dementia paralytica.

4. The demonstration of these small lesions in the cortex and the spinal cord in diffuse sclerosis shows that there are forms of diffuse sclerosis that resemble disseminated sclerosis so closely that in the absence of etiologic knowledge they cannot be distinguished from it.

CONGENITAL HYPOPLASIA OF THE OLIVO-PONTOCEREBELLAR TRACTS

H. M. ZIMMERMAN, M.D.
AND
KNOX H. FINLEY, M.D.
NEW HAVEN, CONN.

Numerous cases are on record of congenital malformations of the cerebellum in man associated with lesions in the pons and inferior olives. Certain ontogenetic generalizations have been drawn from these experiments of nature that have helped greatly in clarifying the related fiber tract connections of these three structures—cerebellum, pons and inferior olives—but considerable lack of agreement still exists. Are the olivocerebellar connections olivofugal or cerebellofugal, or both? Do the inferior olives stand in direct connection with the cerebellar cortex or rather with the dentate nuclei? Are there connections of the olives and accessory olives with the paleocerebellar cortex and with the central cerebellar medullary nuclei? These and many other questions of equal import still lack uncontroverted answers.

Little work of an experimental nature has been done up to the present in attempting to clarify these fundamental problems and work of this kind is beset with a number of almost insurmountable difficulties. Chief among them is the fact that any attempt at mechanical ablation or destruction of a single nuclear mass or fiber tract necessarily results in injury to contiguous structures. Study of such material by methods involving degeneration is beset with difficulties of interpretation. As often as not also, as for example in lesions of the inferior olives, no clearcut changes are produced in distant but related structures.

It seems, therefore, that those instances in man in which congenital lesions are limited to a single system, or to easily definable systems when more than one are involved, offer the choicest material for anatomic analysis. Less has been accomplished from an interpretative standpoint in some of the previously reported cases of this nature than might have been because the majority were not instances of the simple involvement of a single system. Indeed, some cases were complicated by, or were the result of, inflammatory or vascular degenerative processes, neither of which often confine themselves to single systems. The case herein

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From the Neurological Study Unit and the Department of Pathology, Yale University School of Medicine, and the New Haven Hospital.

reported, however, is not subject to these criticisms, and for this reason has perhaps unique value. In addition, it presents the rather unusual feature of a paleocerebellar hypoplasia involving the vermis, the flocculus and some of the central cerebellar nuclei.

REPORT OF A CASE

Clinical History.—C. J., a girl infant, was the product of the only pregnancy of a mother aged 41 and a father aged 45. The pregnancy had been complicated by nephritis, which necessitated delivery by cesarean section during the eighth month. The infant at birth weighed 1,600 Gm. Her head was unusually large and she had a spina bifida in the sacral region, which had been satisfactorily repaired. She was breast fed without difficulty, seldom vomited, and at the end of three months had gained 1,600 Gm. in weight. In the meantime, the head progressively increased in size, and the lower extremities were observed to be rigid and flexed on the abdomen.

When first seen in the pediatrics dispensary on Feb. 8, 1927, at the age of 3 months, the baby was somewhat undernourished. The head was large (occipitofrontal diameter 41 cm.) and out of all proportion to the size of the face. The cranial sutures were widely separated, and the fontanels were abnormally large, the anterior measuring 4 by 3 cm., and the posterior 2 by 2 cm. The eyes converged inward and were sunken in the orbital cavities. The upper extremities were rigid and resisted passive movement, yet at times they were moved voluntarily. Usually the forearms were held rigidly flexed at the elbows. The lower extremities were even more rigid than the upper and were flexed at the knees and hips. They were not observed to move voluntarily. Passive movement of these extremities was limited to 10 degrees in the left knee and 15 degrees in the right. Deep reflexes could not be obtained because of the marked rigidity. The extensor Babinski and the Kernig phenomena were negative; von Graefe's sign was positive. There was no ankle clonus. A course of muscle training at biweekly intervals was started in the orthopedic department. The head progressively enlarged during the next ten months, the occipitofrontal measurement increasing to 47.8 cm. on September 28.

For a week prior to admission to the hospital on Dec. 3, 1927, the child vomited daily, refused food and appeared ill. No fever was noted. Five hours before admission, the parents became alarmed because the child was breathing with difficulty, and for this reason they brought her to the accident room of the hospital. Respirations were irregular and jerky. A convulsion occurred involving the eye muscles, the right side of the face and the right upper extremity. Examination revealed a further increase in the size of the head but no other significant findings. The temperature suddenly rose to 104 F., and the child died twelve hours after admission. Only a small amount of fluid was obtained from a lumbar puncture shortly before death, but a ventricular puncture yielded 30 cc. of clear fluid with a count of 6 cells per cubic millimeter.

Necropsy.—Gross Description: The body was that of a well nourished infant measuring 69 cm. in length and weighing 6,550 Gm. The head was unusually large, and particularly marked was the protrusion of the brow. The cranial sutures were widely separated and the anterior fontanel measured 3 by 5 cm. Over the first sacral vertebra was a puckered scar, measuring 3 cm. in diameter. The remaining description will be confined to the central nervous system to which the abnormal findings were limited.

The brain was removed intact in the dura after the head had been embalmed. During the removal a large amount of cerebrospinal fluid escaped from the small tears in the dura incident to its separation from the cranial bones. Formaldehyde was injected into each of the two lateral ventricles, and the whole brain was further fixed in this fluid. On section of the brain, several unusual and interesting features were observed (fig. 1). Both lateral ventricles were tremendously dilated, each having a capacity of several hundred cubic centimeters. It was obvious that the dilatation of the ventricles was practically entirely at the expense of the white matter, the cortical gray matter showing no obvious decrease in width. The septum lucidum was thin in some regions and wanting in others, thereby allowing a direct communication between the two lateral ventricles. No cause for the hydrocephalus was found as far as the choroid plexuses were concerned, since they were of normal size for an infant of this age. The third ventricle was moderately dilated, as was the rostral portion of the aqueduct of Sylvius. The remaining part of the aqueduct was neither obstructed nor abnormally dilated. The fourth ventricle, although slightly misshaped, was undilated. As

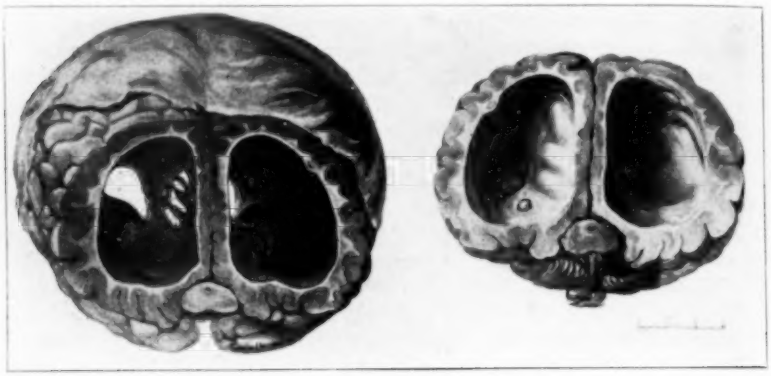

Fig. 1.—A section of the brain showing a marked hydrocephalus, chiefly at the expense of the white matter. Note the defects in the septum lucidum and the nodules of gray matter projecting into the ventricles.

far as could be determined, the foramina of Luschka and Magendie were patent. The corpus callosum was thin, measuring only 3 mm. in thickness. The corpora striata also suffered as a consequence of the greatly dilated ventricles. Small nodules of gray matter, varying in size and shape, projected into the ventricles through the thin white matter.

The left cerebellar lobe was very small, being only about from one-third to one-fourth the size of the right cerebellar lobe, and was covered with blood from a recent hemorrhage (fig. 2, *A* and *B*). The lobular structure of the cerebellum was indistinct. The atrophy of the left cerebellar hemisphere involved particularly the superior, lateral and rostral portions. The inferocaudal part of this lobe was less atrophic (fig. 2, *C*), but the left cerebellar tonsil was smaller than the right. The flocculi were not visible on either side. Most interesting was the apparent complete absence of the vermis both on external examination and on section. Another startling anomaly was the small size of the pons and the middle cerebellar peduncles. The size and arrangement of the blood vessels at the base of the brain were normal.

The entire cord was removed together with the intact dura and the lower lumbar and the sacral vertebrae. The caudal end of the spinal dura was ballooned out to form a sac containing cerebrospinal fluid. Anteriorly, this part of the dura was intact, but posteriorly, opposite the body of the first sacral vertebra, was a hiatus from 2 to 3 cm. in length. This hiatus was filled in by dense scar tissue, which underlay the puckered scar of the skin previously mentioned.

Microscopic Description: Serial sections were made of the brain stem and the attached intact cerebellum. The block of tissue included the rostral three fourths of the medulla oblongata, the pons, the cerebellum, the midbrain and the caudal portion of the hypothalamic region. The material was embedded in paraffin, sectioned at 20 microns, and stained with Heidenhain's iron-hematoxylin after mordanting in Zenker's fluid.

Preparations of the medulla showed a striking difference in the size of the two inferior olives. The right olivary body was the smaller, being approximately one-half the size of the left. In the more rostral sections of the medulla, the

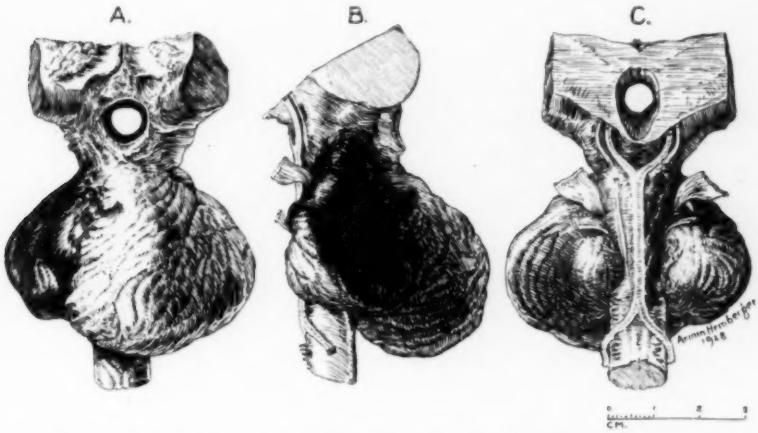

Fig. 2.—*A*, dorsal view of the cerebellum showing aplasia of the left cerebellar hemisphere (covered with blood from a recent hemorrhage) and apparent absence of the vermis. The central opening represents the interpeduncular fossa. *B*, left lateral view of the cerebellum emphasizing the inequality in size of the two cerebellar hemispheres. *C*, ventral view of the brain stem showing the inconspicuousness of the pons and the middle cerebellar peduncles.

right inferior olive was entirely absent, while the left could be followed to the junction of the pons and medulla (fig. 3). That portion of the median raphé which lies between the two olives was displaced to the right because of the marked inequality in size of the two latter structures. The ventral parts of both inferior olives were indicated only in outline; the few cells present were small and atrophic. The remaining portions of the inferior olives contained normal cells. The dorsal accessory olives were both decidedly aplastic, and the right was smaller than the left. Both median accessory olives were malformed and contained but few ganglion cells, which were small and poorly developed. The fibers coursing through the hilus of the small olive were distinctly fewer than those on the contralateral side. This quantitative difference in the olivocerebellar fibers of the two sides could be followed into the restiform bodies. The right olivocerebellar

component of the internal arcuate fibers (associated with the left normal olive) was definitely greater than that of the corresponding fibers of the contralateral side. Likewise, the right restiform body was distinctly larger than on the left (fig. 3).

The pyramidal tracts, as they were followed through the medulla, were observed to be of unequal size. The right tract was slightly though definitely smaller than the left, the former measuring 15 by 8.5 mm. in cross-diameter, and the latter 18 by 8.5 mm. Degenerated fibers were not observed. The median

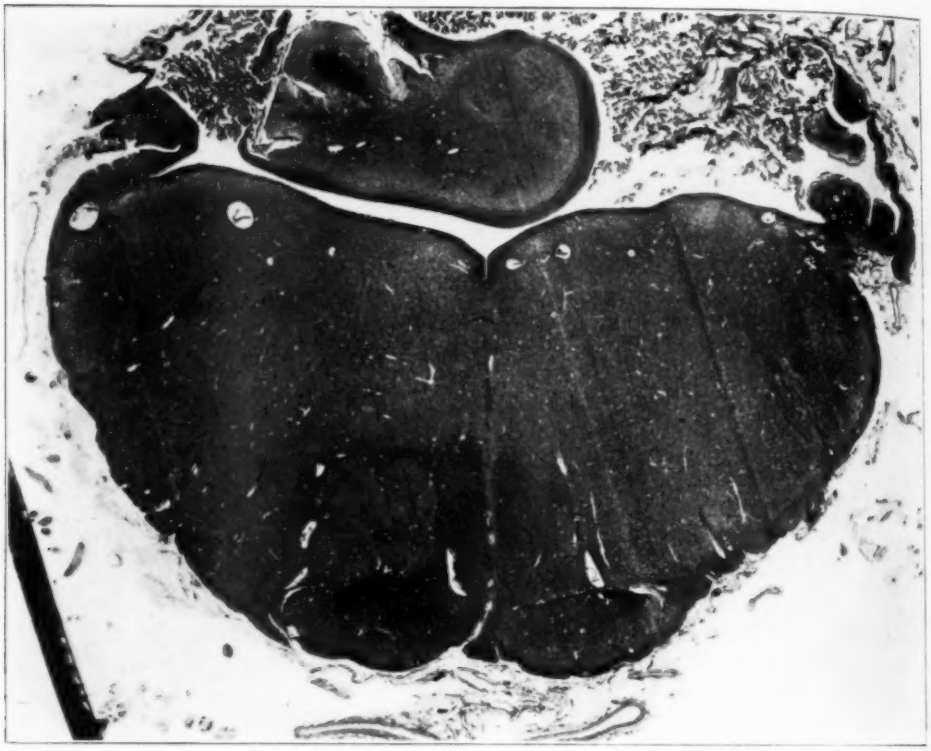

Fig. 3.—A section of the rostral end of the medulla showing absence of the right inferior olive.

raphé in the region of the pyramidal tracts was curved toward the right because of the inequality in the size of these two fiber systems.

The external arcuate nuclei were present bilaterally and were of equal size. The external arcuate fibers were visible on both sides, but in some sections appeared more numerous on the left. The dorsal parasympathetic nucleus of the glossopharyngeal nerve was represented on the left by a well defined group of medium-sized ganglion cells, but on the right it was practically absent, only an occasional cell remaining. Likewise, the right nucleus ambiguus contained many large ganglion cells, while the opposite nucleus had only a very small number. Fibers arising from these two nuclei and coursing toward the floor of the fourth ventricle were definitely more numerous on the side of the larger nucleus. The

remaining motor cranial nerve nuclei (including the oculomotor) and their fibers were normal bilaterally.

Very striking was the large number of nerve cells in the left nucleus of Deiters (the side of the large olive), in contrast to the partial absence of cells in the contralateral structure; in several of the preparations there were no nerve cells visible on the right side. The caudal end of the dorsal acoustic nucleus appeared better developed on the left, although both nuclei were present. In the more cephalic levels, however, these nuclei were equally well developed on the two sides. The superior olives, trapezoid nuclei, trapezoid body and lateral lemnisci were equally well developed bilaterally. The medial lemniscus and the

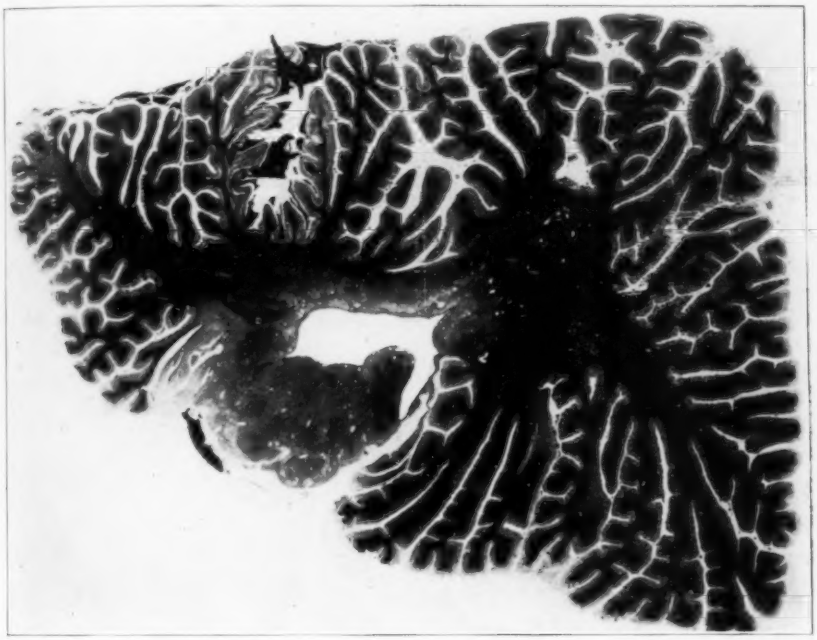

Fig. 4.—A complete transverse section of the cerebellum. Note the atrophic left cerebellar hemisphere and left dentate nucleus.

posterior longitudinal fasciculus appeared normal. The spinocerebellar and the rubrospinal tracts were not sharply outlined, and hence possible variations in their magnitude were not discerned.

Serial sections containing the cerebellum showed clearly the marked difference in the size of its two hemispheres (fig. 4). The left hemisphere, besides being much reduced in size, was made up of lobules that were not only smaller and less numerous, but also much less complex in structure. There was much less branching of the individual lobules to form secondary lobules. Many of the primary lobules projected from the medullary core of the hemisphere as tonguelike processes. There was a noticeable absence of granular and Purkinje cells in the aplastic portions of the cerebellum, i. e., the left hemisphere and vermis (fig. 5). The granular layer was much paler and the distance between Purkinje cells greater as compared with the normal right hemisphere (fig. 6). Although the

vermis was not seen in the gross, it was visible in the microscopic preparations as a markedly atrophic and maldeveloped structure. The nodulus was present in the more caudal sections, but was abnormally small and displaced to the right. In general, it may be said that the left half of the vermis was more atrophic than the right. These malformations and atrophies were most prominent in the lingula of the cerebellum. Lying in the medullary substance of the cerebellum, between the roof of the fourth ventricle and the malformed vermis, were two circumscribed and highly atypical structures (fig. 7). Purkinje and granular cells in moderate numbers occupied these formations, but lacked an orderly arrangement. Single Purkinje cells and small islands of granular cells were frequently

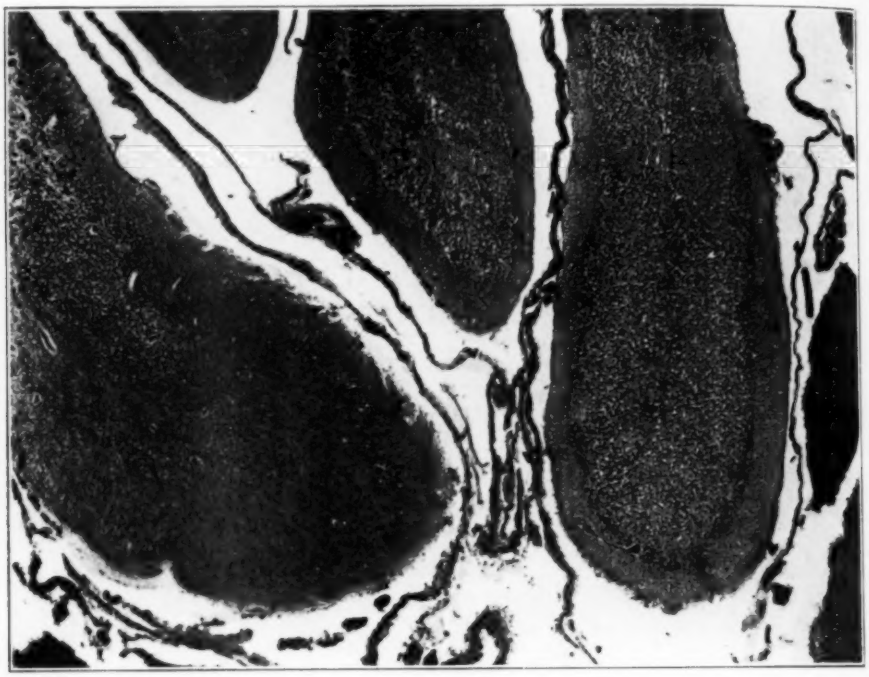

Fig. 5.—A photomicrograph of the left flocculus showing atrophic lobules and aplasia of the granular and Purkinje cell layers; × 65.

noticed lying isolated. More commonly, however, distorted islands of granular cells were bordered by Purkinje cells. These structures suggested cerebellar cortex and represented heterotopias. In some of the sections, these cortical anomalies were continuous with the cortex of the aplastic vermis.

The left tonsil of the cerebellum was smaller than the right. The cortex of the former was underdeveloped, containing fewer granular and Purkinje cells than the latter. This was particularly true of the most medial lobule. Both cerebellar flocculi were atrophic and malformed as regards their Purkinje and granular cell layers. The changes observed here were in all respects comparable to those in the left cerebellar hemisphere. The right flocculus appeared even more atrophic than the left.

The left dentate nucleus was much reduced in size in all dimensions (fig. 4). The right dentate could be followed for a greater distance in both the caudal and the cephalic sections. It was estimated that the dentate nucleus of the small hemisphere was only one-third the size of the opposite nucleus. All the ganglion cells present in the aplastic nucleus appeared normal, and there were no heterotopias in direct connection with it. However, just medial to this nucleus was found a small group of nerve cells which resembled to some degree those present in the dentate nucleus, but which lay entirely isolated in the white matter. Other collections of cells of a similar nature were present medial and ventral to the right dentate nucleus. Although these cells lay in the general region of the central

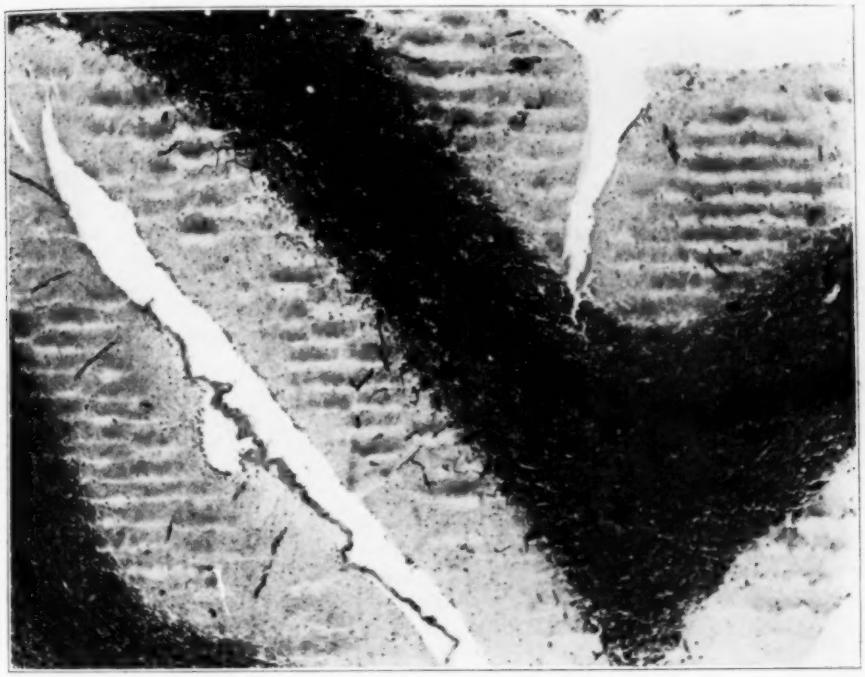

Fig. 6.—A photomicrograph of the cerebellar lobules of the normal right hemisphere at the same magnification as that shown in figure 5.

cerebellar nuclei (nuclei emboliformes, globosi and fastigii), the unusual arrangement of the cells within each group and the fact that the groups did not lie in corresponding positions bilaterally was evidence against their being these structures. They were probably heterotopias.

At the level of the outgoing fibers of the sixth nerve, a few of the pontile nuclei appeared ventral and lateral to the left pyramidal tract. None was present on the right at this level. Slightly more cephalic, other pontile nuclei made their appearance on the left, ventral to the median lemniscus. A few pontile cells were present on the right, but they were distinctly fewer than those on the contralateral side. At a level through the middle of the pons, the greater abundance of the pontile nuclei on the left over those on the right was striking. However, the greater number of transverse pontile fibers on the right over those on the left was

just as striking. The absence of the normal number of pontile ganglion cells on the right on the one hand, and the decrease in the number of pontocerebellar fibers on the left on the other hand, had decreased the cross-section area of the pons on both sides by about one-half. As might be expected from the large number of pontocerebellar fibers on the right, the right middle cerebellar peduncle was about twice the size of the opposite middle peduncle. The median raphé of the pons, both its ventral pontile and dorsal tegmental portions, was displaced to the right. The fourth ventricle was deformed into an elliptical cavity pointing upward and to the right.

The superior cerebellar peduncle originating from the smaller dentate nucleus and cerebellar hemisphere (left side) was about one-third the size of the similar

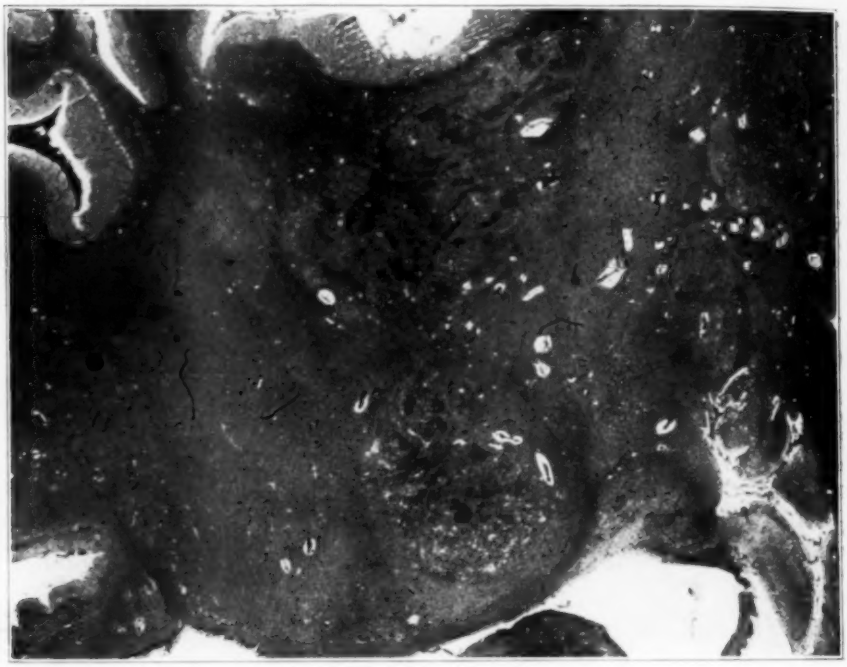

Fig. 7.—A photomicrograph of the meduliary substance of the cerebellum above the roof of the fourth ventricle, showing the two large cerebellar cortical heterotopias; × 12.

peduncle arising from the normal cerebellar hemisphere (fig. 8). At their point of decussation in the midbrain, many more fibers were seen crossing the midline from the right to the left than in the reverse direction. Cephalic to the decussation, the larger peduncle lay on the opposite side, i. e., to the left of the midline, and the smaller to the right. These two fiber bundles were seen terminating in the red nuclei. The left red nucleus was possibly slightly larger than the right, but there was no appreciable difference between the numbers of large and small ganglion cells within the two nuclei. However, the left red nucleus contained many more fibers than the right.

The left cerebral peduncle was definitely larger than the right, which is not readily explainable on the basis of the hydrocephalus (resulting in atrophic or

aplastic changes in the pyramidal systems), as the hydrocephalus involved both lateral ventricles to an equal degree. The smaller number of the cerebropontile fibers on the right side, associated with the fewer pontile ganglion cells on the right, may be the factor underlying the smaller right peduncle.

Summary of Anatomic Observations.—There was a communicating hydrocephalus with which was associated some inequality in development of the right pyramidal tract. The whole left cerebellar hemisphere was atrophic and to a certain degree malformed, and sharing in the atrophy was also the left dentate nucleus. The ventral and dorsal parts

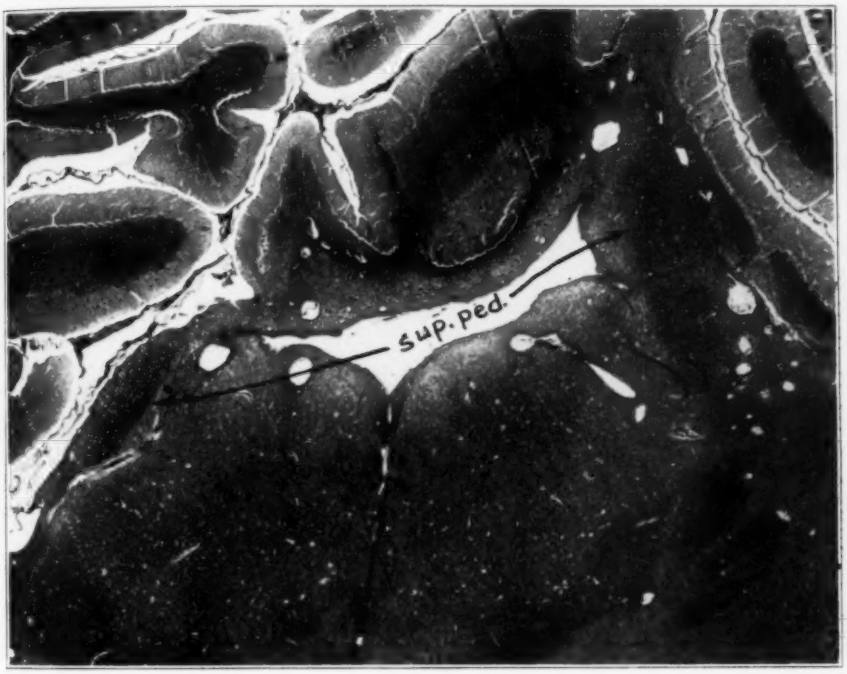

Fig. 8.—A photomicrograph at the level of the superior cerebellar peduncles (sup. ped.) showing the difference in size between the two; × 15.

of the vermis suffered similar and even more extensive changes, the left half of the vermis more so than the right. Both cerebellar flocculi and the medial portion of the left tonsil were similarly involved, and in addition, the left tonsil was smaller than the right. The central cerebellar nuclei (globosi, fastigii and emboliformes) were completely absent or at least poorly developed. Cortical heterotopias were found in the central white matter of the cerebellum above the roof of the fourth ventricle. The right inferior olive was atrophic and the ventral limbs of both olives had but a few small cells. The median accessory

olives were maldeveloped bilaterally. Both dorsal accessory olives were aplastic; the left was smaller than the right. These olivocerebellar relationships are indicated graphically in figure 9.

The right olivocerebellar fibers (from the left normal olive) were more numerous than the left, and as a result the right restiform body

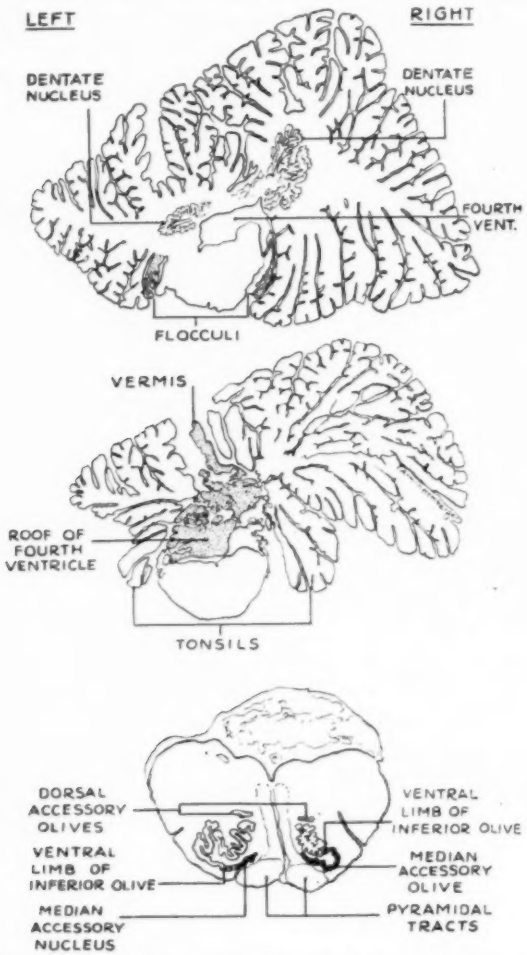

Fig. 9.—Schematization of the cerebellar and olivary relationships in this case. The stippled zones represent aplasias; the shaded zones represent more severe maldevelopment.

was also larger. The right middle cerebellar peduncle was about twice the size of the left as a result of the more numerous ganglion cells on the left side of the pons. The left superior cerebellar peduncle was much smaller than the right, having its origin from the smaller cerebellar hemisphere with its atrophic dentate nucleus. Again, the right red

nucleus was definitely smaller than the left, the reason for this obviously being the fact that this nucleus received fewer fibers from the smaller superior cerebellar peduncle after its decussation in the midbrain.

There was a decrease in the size of the right lateral vestibular nucleus of Deiters, but no positive differences in size of the other pairs of vestibular nuclei were established. The acoustic nuclei and the superior olives with their related fiber tracts were equal in size bilaterally. Unaccountable findings were the abnormally small right dorsal glossopharyngeal and left ambiguus nuclei.

COMMENT

It is fair to state, perhaps, that the clinical symptoms presented by this patient can be adequately explained on the basis of the anatomic conditions of congenital communicating hydrocephalus associated with the spina bifida. What rôle the olivopontocerebellar lesions had to play in contributing to the spastic paralysis of the extremities must remain a moot question in view of the presence of hydrocephalus. Nor can the partial aplasia of the right pyramidal tract in itself be held responsible for this condition, as the paralysis was bilateral.

There is significance in the fact that the conditions of spina bifida and hydrocephalus were noted at birth in this child, who was delivered in the eighth month of pregnancy. This points to an early congenital malformation and presents also an explanation of the hypoplasia of the inferior olives, pons, cerebellum and their connections. That no other causes, such as vascular changes and inflammatory processes, could be held responsible for this condition is obvious from the gross as well as from the histologic observations. Of great interest, moreover, is the fact that a part of the cerebellum which is involved (vermis and central cerebellar nuclei) belongs to the paleocerebellar structures. The great majority of the instances of cerebellar aplasia previously reported have been confined to the neocerebellar structures. Obersteiner,[1] however, reported a case of paleocerebellar involvement in which there was an absence of the anterior medullary velum, the lingula, flocculi and the nuclei fastigii, together with a malformation of the vermis. Although the concept of a division of the cerebellum into neo and paleo portions appears to be well supported both ontogenetically and phylogenetically, there are some dissenting views. Marburg [2] was strongly of the opinion that such a sharp division of the cerebellum is impossible because the vermis, as well as the cerebellar hemispheres, is very closely related to

1. Obersteiner, H.: Ein Kleinhirn ohne Wurm, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **21**:124, 1914-1916.

2. Marburg, O.: Das Kleinhirn beim angeborenen Hydrocephalus. Ein Beitrag zur Pathogenese der angeborenen Kleinhirnerkrankungen, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **21**:213, 1914-1916.

the pons. If there is justification for the views of Winkler,[3] who believed that no sharp demarcation between paleocerebellar and neocerebellar structures exists, but that one may be interpolated into the other, Marburg's objections are overcome. And yet, in the case reported here, the structures usually classed as paleocerebellar are much more involved than is even the neocerebellar left hemisphere. To account for this paleocerebellar lesion there must be assumed an inhibitory influence very early indeed in embryonic development; but why should the neocerebellar structures then have been involved relatively so little?

Since 1829, when Cruveilhier first described the condition, it has been known that unilateral cerebral lesions often result in atrophy of the contralateral cerebellar hemisphere. A group of such cases has been described by Kononova.[4] In the paper by Marburg already quoted, the statement appears that the cerebrocerebellar connections are not alone with the lateral lobes, but also with the vermis. The changes in the left cerebellar lobe and in the vermis in the case under discussion could then be attributed to a primary cerebral lesion but for the fact that the hydrocephalus produced equal damage to both cerebral hemispheres, and only the left cerebellar lobe was involved. Moreover, cerebellar lesions as in this case are rare as contrasted with the rather frequent occurrence of congenital hydrocephalus. For these reasons, therefore, it seems justifiable to assume that the cerebellar changes are independent of the cerebral condition.

It has been tacitly, and more or less arbitrarily, assumed in our case, that the unilateral pyramidal tract atrophy was somehow linked to the hydrocephalus. It is of interest to note, therefore, that certain writers hold that there is a cerebellopyramidal tract connection. Krause [5] cited a case of bilateral cerebellar atrophy with partial loss of the central white matter and the central cerebellar nuclei, in which there were an absence of both pyramidal tracts and a generalized atrophy of the cerebral hemispheres. Messing [6] reported a less lucid instance of right cerebellar atrophy with complete absence of both pyramidal tracts, but there was present a left cerebral porencephaly. Another such example was described by Redlich,[7] in which there was a cerebellar cortical

3. Winkler, C.: A Case of Olivo-Pontine Cerebellar Atrophy and Our Conceptions of Neo- and Paleo-Cerebellum, Schweiz. Arch. f. Neurol. u. Psychiat. **13**: 648, 1923.

4. Kononova, É.: L'atrophie croisée du cervelet, Thèse, Paris, 1911-1912.

5. Krause, F.: Ueber einen Bildungsfehler des Kleinhirns und einige faseranatomische Beziehungen des Organs, Ztschr. f. d. ges. Neurol. u. Psychiat. **119**: 788, 1929.

6. Messing, Z.: Drei Fälle von Porencephalie, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **11**:184, 1904.

7. Redlich, E.: Demonstration mikroskopischer Präparate eines Falles von diffuser Kleinhirnsklerose, Wien. klin. Wchnschr. **28**:647, 1896.

sclerosis involving also the central white matter, but not the central nuclei, as well as an atrophy of the ventral part of the pons, the olives and the pyramidal tracts. In commenting on this case of Redlich, Obersteiner suggested that the pyramidal tracts may have been involved by the diffuse sclerosis in their passage through the pons. Experimentally, Biedl (quoted by Redlich) found that after section of the restiform bodies there resulted a degeneration of the ventral fibers of the lateral pyramidal tract on the ipsolateral side. In our case, the restiform body was atrophic on the left side and the pyramidal tract on the right side. From this recital of the anatomic evidence for a direct connection between the cerebellum and the pyramidal tracts, considerable doubt of its existence must arise. Only Biedl's work seems to support it, but that work needs confirmation.

The fiber tract connections of the inferior olives are little understood. Most writers hold that these tracts are olivofugal, some asserting that they go to the cerebellar cortex and others maintaining equally strongly that they go to the dentate nuclei. A not inconsiderable number of writers, on the other hand, attempt to prove that cerebellofugal tracts taking origin either from the cerebellar cortex or from the dentate nuclei connect the cerebellum to the olives. It has been suggested even that there are both olivofugal and cerebellofugal connections between these structures. Practically all workers, however, are unanimous in their belief that these are crossed connections; only a very small minority maintain that in addition to the crossed connections there exists a small ipsolateral bundle of nerve fibers.

Olivocorticocerebellar Tracts.—The strongest supporters of an olivocorticocerebellar (olivofugal) tract are Brouwer [8] and Holmes and Stewart,[9] who stated that the olives send their axis cylinders to the opposite cerebellar lobes and not to the cerebellar nuclei. Moreover, they believed that there is a definite regional relationship between the different portions of the inferior olives and the different areas of the cortex of the cerebellum; the dorsal olivary loops are connected with the dorsal cerebellar cortex, the ventral with the ventral part, the medial with the medial, and the lateral with the lateral part of the cortex. Brouwer also quoted Bruns as stating that the inferior olives send fibers to the uncrossed cerebellar cortex by way of the homolateral restiform body. These fibers take origin from the dorsal portion of the olive. Experimentally, Russell [10] found, after removal of

8. Brouwer, B.: Ueber Hemiatrophia neocerebellaris, Arch. f. Psychiat. **51**: 539, 1913.

9. Holmes, G., and Stewart, T. G.: On the Connections of the Inferior Olives with the Cerebellum in Man, Brain **31**:125, 1908.

10. Russell, J. S. R.: Degeneration Consequent on Experimental Lesions of the Cerebellum, Phil. Tr. London (B) **186**:633, 1895.

one lateral lobe of the cerebellum, that degenerated fibers in the inferior cerebellar peduncle passed to the opposite inferior olive. No mention is made of any possible damage to the dentate nuclei in these animals. This finding also does not rule out the possibility that the degenerated fibers are cerebellofugal; it merely establishes the fact of a cerebello-olivary connection.

Olivodentate Tracts.—Vogt and Astwazaturow [11] showed that in spite of cortical cerebellar lesions the inferior olives can be normal, and that only in dentate nuclear lesions are the olives affected. Indeed, these writers were convinced that a cerebellar cortical atrophy in itself does not produce changes in the olives, and that when such changes in the olives occur, they are associated with dentate nuclear lesions. This view was shared by Schaffer.[12] Writing in 1912, Vogt and Astwazaturow stated that there were no examples in the literature of damage to the dentate bodies in which the crossed inferior olives had remained normal. They did state, however, that the olives can atrophy independently of the dentate nuclei by a descending degeneration of the central tegmental tract of Bechterew.

Dentato-Olivary Tract.—On the other hand, Marburg, writing in 1914, was authority for the statement that cases have been reported of lesions in the dentate nuclei without olivary involvement, and on this basis he argued for a connection between the olives and the cerebellar cortex as well as the dentate nuclei. Winkler, in a paper in 1923, cited a case of atrophy of the olivary and pontile nuclei with intact dentate nuclei, but with atrophy of the cerebellar cortex, particularly of the granular layer, and thus supported Marburg's contention of a connection between the olives and the cerebellar cortex. Schaffer elaborated this view by stating that there are two tracts connecting the olives to the cerebellum: (1) an olivocerebellar tract, which ends in the cerebellar cortex, and (2) a cerebello-olivary tract, arising in the dentate nuclei and ending in the ganglion cells of the olives—a dentato-olivary tract. The latter follows the olivocerebellar tract, the two going in opposite directions. Schroeder and Kirschbaum [13] drew from an analysis of a case that they described the conclusion that there is no

11. Vogt, H., and Astwazaturow, M.: Ueber angeborene Kleinhirnerkrankungen mit Beiträgen zur Entwickelungsgeschichte des Kleinhirns, Arch. f. Psychiat. **49**:75, 1912.

12. Schaffer, K.: Gibt es eine cerebello-olivare Bahn? Ztschr. f. d. ges. Neurol. u. Psychiat. (O.) **30**:70, 1915. Ueber einige Bahnen des menschlichen Rhombencephalons, ibid. **46**:60, 1919.

13. Schroeder, A. H., and Kirschbaum, W.: Ueber eigenartige degenerative Erkrankungen des Zentralnervensystems mit vorwiegender Beteilung des olivocerebellaren Systems und Grosshirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:681, 1928.

evidence for a dentato-olivary tract, but rather for an olivodentate (olivofugal) tract. Schaffer's opinion of a cerebellofugal tract arising in the dentate nuclei and going to the olives was supported in a paper by Mingazzini and Giannuli.[14] These workers admitted, however, the possibility of an olivocerebellar tract (olivofugal), but stated that it must be a small one. This work, then, represents about all the evidence that there is in support of a dentato-olivary tract.

Corticocerebello-Olivary Tract.—As regards a corticocerebello-olivary tract, Koelliker (quoted by Schaffer) stood practically alone in his belief that there are cerebello-olivary fibers representing a cerebellofugal system and consisting of Purkinje cell fibers that end around the olivary cells. From this avalanche of conflicting and often contradictory evidence one conclusion only seems permissible and that is that an olivocerebellar (olivofugal) tract exists, but whether it ends in the cerebellar cortex or in the dentate nuclei, or perhaps in both, is not a settled question.

Connections Between Accessory Olives and Cerebellum.—Holmes and Stewart[9] and Brouwer and Coenen[15] studied the relationships of the accessory olives to the cerebellum, and concluded that the dorsal accessory olives send fibers to the dorsal paleocerebellar cortex, and that the median accessory olives send fibers to the ventral paleocerebellar cortex (pyramis, uvula, nodulus, flocculus and paraflocculus). Masuda[16] likewise stated that the median accessory olives (and the ventral halves of the inferior olives) are connected with the deep and caudal parts of the vermis. A somewhat similar view was held by Mingazzini and Giannuli, namely, that there is a tract connecting the inferior part of the vermis and the proximal part of the median accessory olives. Directly contradicting these views, however, is the case reported by Spiller,[17] in which were present a cerebellar atrophy and sclerosis involving the vermis as well as the lateral lobes and implicating the inferior olives, but completely sparing the accessory olives. What relationship, if any, exists between the accessory olives and the nuclei emboliformes, tecti (fastigii) and globosi is apparently not known. These medullary nuclei are even less well understood than are the

14. Mingazzini, G., and Giannuli, F.: Klinischer und pathologisch-anatomischer Beitrag zum Studium der Aplasiae cerebro-cerebellospinales, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:521, 1924.

15. Brouwer, B., and Coenen, L.: Ueber die Oliva inferior, J. f. Psychol. u. Neurol. **25**:52, 1919-1920.

16. Masuda, N.: Ueber das Brückengrau der Menschen (Griseum Pontis) und dessen nähere Beziehungen zum Kleinhirn und Grosshirn, Arb. a. d. hirnanat. Inst. in Zurich **9-10**:1, 1914.

17. Spiller, W. G.: Four Cases of Cerebellar Disease (One Autopsy) with Reference to Cerebellar Hereditary Ataxia, Brain **19**:588, 1896.

olives, although Herrick[18] stated that the nucleus fastigii receives direct vestibular root fibers, fibers from the vestibular nucleus, from the cortex of the vermis and probably also from the basal vestibular cortex. Its efferent fibers are distributed to the nuclei of the medulla oblongata and midbrain. The nuclei emboliformes and globosi receive fibers from the cerebellar cortex (chiefly from the hemispheres) and give rise in part to the brachium conjunctivum.

Let us now see how far the changes observed in our case can be correlated with the observations mentioned in the foregoing paragraphs. The atrophy of the right inferior olive was undoubtedly associated with that of the left cerebellar hemisphere, but the left dentate nucleus was also atrophic, and hence it is impossible to associate the change in the olive positively with the one or with the other of these. Nor can any conclusion be drawn as to the direction of the fiber tracts, whether they are olivofugal or cerebellofugal. It is interesting that in the presence of an almost complete aplasia of the dorsal part of the vermis, the dorsal accessory olives are likewise strongly aplastic. And in the same manner, the aplasia of the ventral part of the vermis can be linked to the aplasia of the ventral accessory olives. These facts seem to be in complete accord with the views of Holmes and Stewart[9] and Brouwer and Coenen,[15] although of course there is again no evidence as to the direction these fiber tract connections take. The atrophy of the ventral limbs of the inferior olives, as it was bilateral, must be linked to the changes in the vermis; a connection between these two structures was suggested by Masuda. It is impossible to associate the atrophic right nucleus of Deiters with either the absent nucleus fastigii or the atrophic left cerebellar hemisphere: in the first instance, because both nuclei fastigii are absent and only one Deiters' nucleus is small; in the second instance, because this nucleus is on the contralateral side of the atrophic cerebellar hemisphere, whereas the vestibulocerebellar tract is an ipsolateral one. Deiters' nucleus, therefore, with the atrophic right dorsal glossopharyngeal and left ambiguus nuclei, belongs to the category of unaccountable observations in this case.

Pontocerebellar Connections.—The pontocerebellar connections are rather well understood—about some of the finer details only is there any disagreement. It was Brouwer's opinion that the pontile ganglion cells send fibers to the neocerebellum and not to the paleocerebellum, but Schaffer believed that the most dorsal fibers of the middle cerebellar peduncle end chiefly in the upper part of the vermis and some in the lower part. Further, it was Schaffer's opinion that the stratum pro-

18. Herrick, C. J.: Origin and Evolution of the Cerebellum, Arch. Neurol. & Psychiat. **11**:621 (June) 1924.

fundum pontis at the trigeminus level forms a tract which goes to the paleocerebellum and deserves the designation even of a "pontopaleocerebellar tract." Marburg and Masuda were in complete agreement on the fact that the pons can be completely destroyed after a cerebellar lesion, particularly if the latter occurs intrafetally. On this basis can be explained the aplasia of the right pontile nuclei in our case—that it is associated with the atrophy of the left lobe of the cerebellum and resulted from the latter. This case does not answer the question of a pontopaleocerebellar connection, as both the neocerebellum and the paleocerebellum were involved. Moreover, with a paleocerebellar aplasia, the resultant atrophy of the pontile nuclei should be bilateral, but it is impossible to determine if this is so on the left side of the pons.

Connections Between Dentate and Red Nuclei.—That the red nucleus undergoes atrophy following a lesion in the contralateral dentate nucleus or in the superior cerebellar peduncle seems to be well established experimentally and on the basis of studies of human material. Russell found that in dogs the fibers that degenerated in the superior cerebellar peduncle on the side from which one lateral lobe of the cerebellum was removed, passed to the opposite side in the posterior quadrigeminal region, most of them apparently ending in the opposite red nucleus. But a few fibers did not cross, and these appeared to end in the red nucleus on the same side as the cerebellar lesion. Uemura [19] described a case of destruction and atrophy of the right cerebellar hemisphere and a portion of the right dentate nucleus, with degeneration of the right superior cerebellar peduncle and the left red nucleus. A somewhat similar case was described by Masuda in which there was atrophy of part of the left cerebellar lobe and of the left dentate nucleus, with complete absence of its anterior part, and degeneration of the anterior two thirds of the right red nucleus, particularly the small cells. According to Marburg, the converse is likewise true, namely, that lesions in the red nucleus and the superior cerebellar peduncle produce an atrophy of slight degree in the dentate nucleus. In our case, no variations were found in the numbers of large and small cells in the two red nuclei. However, the left red nucleus contained many more nerve fibers than the right, and these could be seen entering the left nucleus from the larger right superior cerebellar peduncle. The generalization can therefore be drawn that the red nucleus is connected with the crossed dentate nucleus by the superior cerebellar peduncle.

19. Uemura, H.: Pathologisch-anatomische Untersuchungen über die Verbindungsbahnen zwischen dem Kleinhirn und dem Hirnstamm, Schweiz. Arch. f. Neurol. u. Psychiat. **1**:151, 1917.

SUMMARY AND CONCLUSIONS

The history is presented of a female infant, aged 13 months, who was delivered in the eighth month of pregnancy by cesarean section because of complicating nephritis in the mother, aged 42. At birth, a spina bifida that was present was repaired, and a hydrocephalus was noted, which increased in severity until the child died. Death occurred with the sudden onset of dyspnea followed by a convulsion of the right side. Throughout life the child had a spastic quadriplegia.

Necropsy revealed a marked communicating hydrocephalus and a fresh hemorrhage over the left cerebellar hemisphere. The latter was atrophic, which was true as well for the left dentate nucleus and the right pyramidal tract. The entire vermis was malformed, and the central medullary nuclei of the cerebellum were absent, being replaced by several cortical cerebellar heterotopias. In association with the cerebellar lesions was an atrophy of the left restiform body, both dorsal accessory olives, the whole right inferior olive, the ventral limbs of both inferior olives, the median accessory olives, the right pontile nuclei and the left middle and superior cerebellar peduncles. There was an atrophy of the right Deiters' and the right dorsal glossopharyngeal and the left ambiguus nuclei.

It is concluded that the atrophy of the right inferior olive was dependent on that of the left cerebellar hemisphere; that the dorsal accessory olives are connected with the dorsal part of the vermis, and that the median accessory olives and the ventral limbs of the inferior olives are connected with the ventral part of the vermis.

Related to the atrophy of the left cerebellar hemisphere was a hypoplasia of the right pontile nuclei and the left middle cerebellar peduncle.

Because the left dentate nucleus was atrophic the left superior cerebellar peduncle, as well as the right red nucleus, was smaller than the corresponding structures of the opposite side. The atrophy of the right nucleus of Deiters and of the right dorsal glossopharyngeal and the left ambiguus nuclei could not be satisfactorily explained or related to the other observations.

NERVE DEGENERATION IN POLIOMYELITIS

III. RATE OF DEPRESSION AND DISAPPEARANCE OF COMPONENTS OF CONDUCTED ACTION POTENTIAL IN SEVERED NERVES; CORRELATION WITH HISTOLOGIC DEGENERATION IN GROUPS OF FIBERS RESPONSIBLE FOR VARIOUS COMPONENTS

PETER HEINBECKER, M.D.

GEORGE H. BISHOP, PH.D.

AND

JAMES L. O'LEARY, M.D.

ST. LOUIS

For purposes of comparison with the degenerating fibers of nerves and roots from monkeys killed during the acute stage of poliomyelitis, it was deemed advisable to study by physiologic and histologic methods normal nerves severed from their cells of origin. Certain histologic changes occurring during the degeneration of cut nerves are well known, but increasing knowledge of the physiology of the fiber types makes possible a more detailed correlation, than has been made thus far, between histologic and functional changes during the course of degeneration.

When the action potential after conduction is recorded by means of the cathode-ray oscillograph, a series of waves is depicted. It has been shown by Bishop and Heinbecker [1] that it is possible to correlate the form of the recorded action potential with the fiber content of the nerve trunk in a manner permitting recognition of the essential fiber type responsible for each potential component. For convenience of reference these components have been named the A, B_1, B_2 and C waves (Heinbecker [2]). The ordinary mixed somatic nerve (sciatic) gives rise to all four. The fibers responsible for the A component are the large, thickly myelinated ones known to include, primarily, somatic motor and sensory elements. The B_1 component includes primarily the somewhat

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From the Departments of Survey, Ophthalmology and Anatomy, the Washington University School of Medicine, St. Louis.

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1. 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.

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

smaller and frequently somewhat more thinly myelinated fibers known to be visceral afferents. These two potential components have characteristic physiologic properties (Heinbecker and Bishop[3]) which permit their differentiation from the B_2 and C components possessing properties of a much slower order. The fibers responsible for the B_2 potential are the smallest, thinly myelinated ones found in the nerve. Unmyelinated fibers give rise to the C potential.

The intention of this investigation has been to determine the time and order of depression and disappearance of the essential components of the action potential and to relate the stages in depression of each component to histologic changes in the fibers responsible.

MATERIAL AND METHOD

Experiments were carried out on fifteen cats and one monkey (Macacus rhesus). Sciatic, radial, genito-femoral, cervical sympathetic and vagus nerves were severed with aseptic precautions at levels that permitted a sufficient length distal to the lesion to be available for study after discarding the area at the point of section. After varying time intervals (from twenty-four to one hundred and twenty hours) the nerves were removed from the body and their action potential recorded if present. In each case the like nerve from the opposite side served as a control.

The cathode-ray oscillograph was used as a recording mechanism in conjunction with an amplifier yielding amplifications up to 200 mm. per millivolt. To stimulate, condenser charges from 1.5 to 150 volts and of a capacity varying from 0.001 to 0.25 microfarad were used. The stimuli were applied through nonpolarizable electrodes, the same type also serving as recording electrodes. The nerves were arranged in a bridge balanced for resistance and capacity as described by Bishop.[4] For the determination of the absolute refractory period, the potentials were recorded after conduction to allow separation out of the waves. Two condensers were connected through two contacts of the circuit breaker and charged in series with the nerve. To prevent the first condenser shunting the second, the circuit breaker was made to open the first circuit before the second was closed, the first condenser charging through the nerve circuit in this interval.

After examinations with the oscillograph were completed (from one to three hours), the nerves with their controls were fixed in 1 per cent osmic acid and in ammoniated alcohol for the silver pyridine (Cajal-Ranson) technic. For the study of infundibular membranes nerve portions were also fixed in the formaldehyde-pyridine-manganese mixtures of Cajal. The preparations were dehydrated, cleared and embedded in paraffin; longitudinal sections at 5 microns were cut from all blocks, and, in addition, cross-sections from the segments that were fixed in osmic acid.

In many mixed nerves the A potential amplitude is five or more times that of the B_1 potential and ten to fifteen times that of the B_2 and C potentials. It is, therefore, a simpler task to compare the rates of disappearance of the B_1, B_2 and C potentials in autonomic nerve trunks where these potentials are of more equal

3. Heinbecker, P., and Bishop, G. H.: Differentiation Between Types of Fibers in Certain Components of Involuntary Nervous System, Proc. Soc. Exper. Biol. & Med. **26**:645, 1929.

4. Bishop, G. H.: The Form of the Record of the Action Potential of Vertebrate Nerve at the Stimulated Region, Am. J. Physiol. **82**:462, 1927.

TABLE 1.—*Conduction Rates, Thresholds and Relative Degrees of Depression of the Potential Components in Nerves Severed from Their Cells of Origin and Normal Controls*

Date	Source	Nerve	Time Cut, Hours	Conduction Distance, Mm.	Thresholds Arbitrary Units				Conduction Rates, Meters per Second				Relative Degree of Depression on Basis of Amplitude				Comment
					A	B_1	B_2	C	A	B_1	B_2	C	A	B_1	B_2	C	
5/ 6/30	Cat	Right radial	12	48	100	600	2,000	5,000	60.0	15.0	10.0	0.5	...	...	...	...	
5/ 6/30	Cat	Left radial	24	48	150	800	2,500	5,000	50.0	10.0	8.0	0.5	...	...	...	...	
6/ 2/30	Cat	Genitofemoral	48	16	300	1,500	2,600	5,000	38.0	1.3	4.5	0.5	3+	4+	2+	1+	4+ indicates greatest degree of depression, 3+ somewhat less, etc.
5/ 8/30	Cat	Left sciatic	91	30	No potentials elicited												
5/ 8/30	Cat	Left sciatic	115	30	No potentials elicited												
5/12/30	Monkey	Left radial	43	48	150	800	3,000	6,000	28.0	11.4	?	0.4	2+	3+	?	1+	B_2 potential too indefinite to measure accurately
5/12/30	Monkey	Right radial	90	48	No potentials elicited												
5/12/30	Monkey	Left sciatic	137	40	No potentials elicited												
5/12/30	Monkey	Right sciatic	186	40	No potentials elicited												
6/ 8/30	Cat	Sympathetic	50	20	...	1,000	4,000	6,000	....	12.5	4.0	0.5	...	3+	2+	1+	
6/ 8/30	Cat	Sympathetic	59	25	...	.....	4,500	6,000	....	....	4.2	0.5	...	...	3+	2+	B_1 potential absent
5/17/30	Cat	Sympathetic	80	20	No potentials elicited												
6/ 2/30	Cat	Vagus	69	23	150	1,500	3,200	5,000	42.0	10.5	4.2	0.6	3+	4+	2+	1+	
6/27/30	Cat	Vagus	72	28	275	.....	?	8,000	31.0	....	?	0.5	3+	...	?	1+	B_1 potential absent; B_2 potential present but separation not adequate to permit accurate measurements
5/17/30	Cat	Vagus	84	33	...	.....	.....	8,000	....	....	....	0.5	...	...	...	2+	A, B_1 and B_2 potentials absent
					Average Normal Controls												
	Cat	Mixed somatic	0	..	100 to 150	400 to 500	1,200 to 2,000	4,000 to 8,000	80 to 50	35 to 15	15 to 10	1 to 0.3	...	...	...	...	Values given for threshold and conduction rates are for the most irritable and fastest fibers of the various groups
	Cat	Vagus	0	..	100 to 150	400 to 500	1,200 to 2,000	4,000 to 8,000	80 to 50	35 to 15	15 to 10	1 to 0.3	...	...	...	...	
	Cat	Sympathetic	0	..	...	400 to 500	1,200 to 2,000	4,000 to 8,000	....	35 to 15	15 to 10	1 to 0.3					
	Monkey	Mixed somatic	0	..	100 to 150	400 to 500	1,200 to 1,600	4,000 to 8,000	35 to 20	18 to 10	10 to 4	0.6 to 0.2					

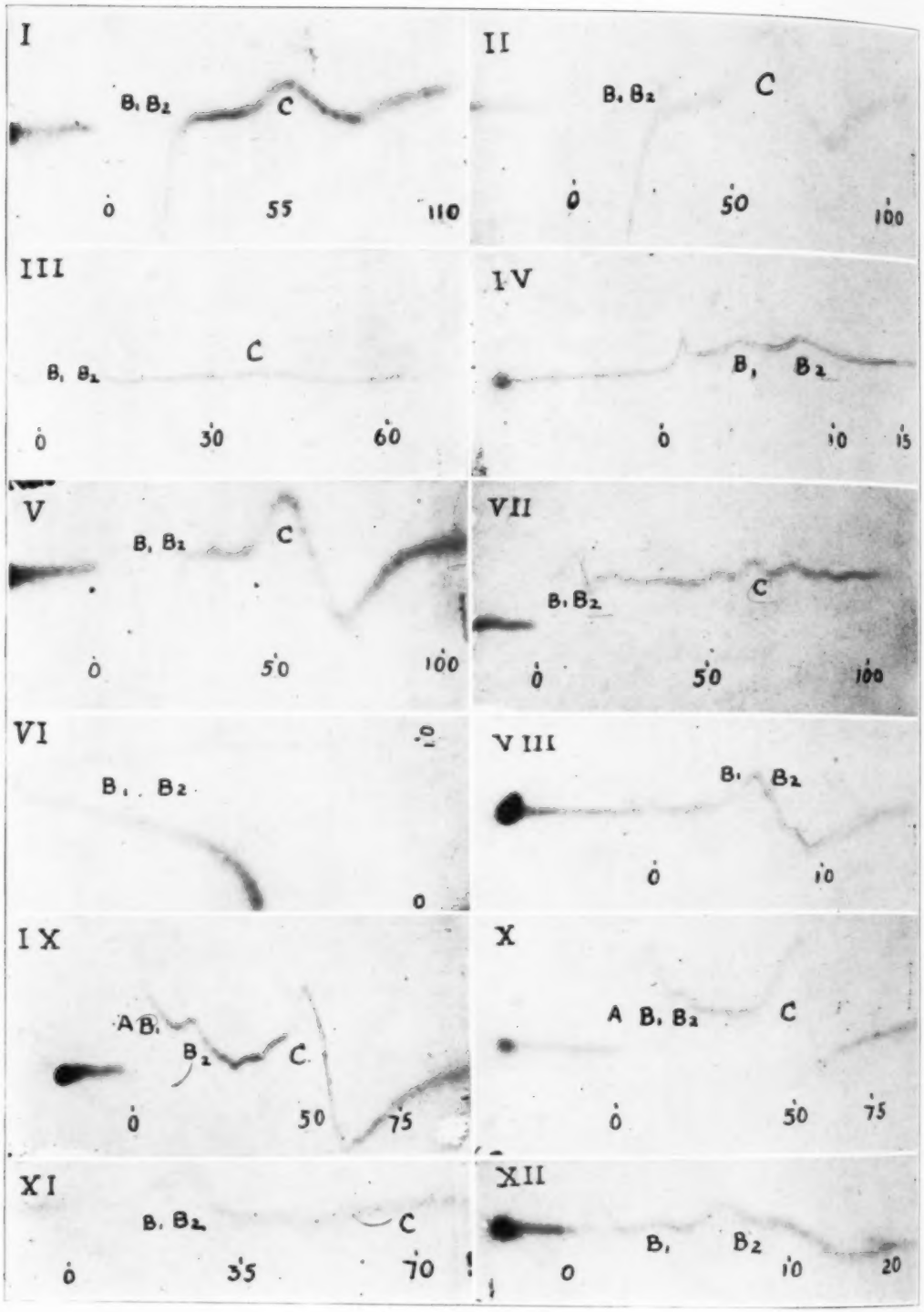
I
B, B2
C
0
55
110
II
B, B2
C
0
50
100
III
C
B, B2
0
30
60
IV
B, B2
0
10
15
V
B, B2
C
0
50
100
VII
B, B2
C
0
50
100
VI
B, B2
0
VIII
B, B2
0
10
IX
A B,
B2
C
0
50
75
X
A B, B2
C
0
50
75
XI
B, B2
C
0
35
70
XII
B,
B2
0
10
20

FIGURE 1

EXPLANATION OF FIGURE 1

Fig. 1.—*I*, conducted action potential through the normal cervical sympathetic nerve of a cat; conduction distance, 29 mm.; temperature, 36 C.; reduced four panel amplification. Time is marked in sigma in this and in subsequent records. A normal control was used for records *III* and *IV*. *II*, same preparation as in *I* with full amplification. *III*, conducted action potential through the sympathetic nerve of a cat cut sixty hours previously. The nerve was taken from the same cat as that recorded in *I*. Conduction distance was 21 mm.; temperature, 36 C. Note low B_1 and B_2 waves; the *C* wave is also much depressed. Ultimately only the depressed *C* potential would persist. *IV*, same preparation as in *III* with faster deflection of the base line to show the first two components better. *V*, conducted action potential through the normal cervical sympathetic nerve of a cat; conduction distance, 25 mm.; temperature, 37.5 C. Normal control for this nerve is shown in *VII* and *VIII*; amplification, four panels reduced. *VI*, same preparation as in *V*, with faster deflection time and full four panel amplification to show maximum magnitude of B_1 and B_2 potential components. *VII*, conducted action potential through a cervical sympathetic nerve cut fifty-nine hours previously; conduction distance, 25 mm.; temperature, 37.5 C.; full four panel amplification. *VIII*, same preparation as in *VII* with faster deflection of the base line to illustrate what remains of the B_1 and B_2 potentials. *IX*, conducted action potential through the vagus nerve of a cat cut seventy-two hours previously; conduction distance, 34 mm.; temperature, 37 C.; full four panel amplification. Normal control for this preparation is shown in *X*. There is some lowering of the potentials of the cut nerve. *X*, conducted action potential through the normal vagus nerve of a cat; conduction distance, 34 mm.; temperature, 37 C. Control for this nerve is shown in *IX*; full four panel amplification. *XI*, conducted action potential through a cervical sympathetic nerve cut sixty hours previously; temperature, 37 C.; full four panel amplification. *XII*, same preparation as in *XI* with faster deflection of the base line. Normal control for this nerve is not shown.

amplitude. It was always easier to compare the rate of disappearance of the A and C potentials in mixed nerves because the C, though lower in amplitude, was invariably present longer than the A. By a correlation of the results obtained in different nerves, it was possible to determine the relative order of susceptibility to degeneration of all the fiber types.

FUNCTIONAL RESULTS

Typical results are tabulated in table 1 and illustrated in figure 1. It was invariably found that the B_1 potential was the first to disappear, next the A potential, then the B_2 and finally the C potential. The B_2 and C potentials persisted from eight to twelve hours longer than the A and B_1 potentials. Interpreted in the light of correlation experiments, this means that myelinated fibers of the somatic system degenerate before myelinated and unmyelinated fibers characteristic of the autonomic system. Small, somatic fibers degenerate before large ones and myelinated, autonomic fibers degenerate before nonmyelinated ones.

It is difficult to state the time at which the first detectable change in the area of the various potential components takes place. Changes in the absolutely refractory period were detectable as early as twelve hours after section of the nerve, but there were no significant changes in potential area before from twenty-four to thirty-six hours. It is also difficult to set absolute values for the times required for the disappearance of the potentials derived from the various fiber types, which would be applicable to all nerves. There were slight variations from nerve to nerve, and also from animal to animal. However, it is possible to state that the B_1 potential disappeared between fifty and seventy hours. The A potential disappeared from five to ten hours later, then the B_2 potential and, finally, the C potential. No C potential has been elicited at a period longer than ninety hours after section of the nerve.

During degeneration, thresholds of the A and B_1 potentials were quickly raised, whereas those of the B_2 and C potentials tended to change much more slowly. In fact, the threshold of the C potential remained relatively low until almost the time of its extinction. Determinations of absolute refractory periods were not obtained in all experiments, but a sufficient number were made to prove that the time of absolute refractoriness is early increased for all potentials. No evidence was obtained to indicate that the absolute refractory periods were ever shortened during the early stages of degeneration, and in this the results differ from those obtained during the early stages of experimental acute poliomyelitis.[5] Slowing of conduction rates of all potentials except the C were shown relatively early, but not quite so readily as the

5. O'Leary, J. L.; Heinbecker, Peter, and Bishop, G. H.: Nerve Degeneration in Poliomyelitis: IV. Physiologic and Histologic Studies on the Roots and Nerves Supplying Paralyzed Extremities of Monkeys During Acute Poliomyelitis, Arch. Neurol. & Psychol., to be published.

changes in refractoriness. The *C* conduction rate, at least for the fastest fibers, remained nearly normal until quite late. The increased temporal dispersion of this potential, however, indicated that slowing of some fibers was present somewhat earlier.

Control nerves from the opposite side of the body were examined in all cases and used as a basis of comparison in estimating the degree of depression of the various potentials. These controls were, however, often kept in Ringer's solution for two or three hours before examination was possible, because of the time consumed in examining the cut nerves. Thus, the conduction rates of the control potentials were not infrequently found to be less than the normal rate of such potentials in fresh nerves, though the areas of potentials were not recognizably altered. Consequently, in the table of results average normal limiting rate values are prescribed for comparison with the rates of degenerating nerves rather than the rate values obtained from the controls.

HISTOLOGIC STUDIES

Decrescence in the physiologic properties of severed nerves is paralleled by early histologic change in the fibers. At the time of disappearance of the action potential, this change has only proceeded to the beginning of the decomposition of myelin (after decomposition it reduces osmic acid following bichromate mordanting and colors intravitally with neutral red). Obviously, therefore, the methods of secondary degeneration are not applicable in the present study, and we must place reliance on the finer criteria of change manifest in osmic and silver preparations.

As in other known processes, loss of function pursues a more rapid course than the histologic evidence of it. At the earliest stage, when significant changes in the potential area were detected, histologic evidence of fiber deterioration was scanty, and it was only by comparison with later stages that we could surely detect such appearances as were retrogressive. But the occurrence of undoubted degenerative changes in a variable number of fibers observed in histologic sections is not a true index of the state of the nerve as a whole. Cajal [6] has previously shown that even when fibers of like size are compared there is a significant difference in their susceptibility to degeneration: some evince early changes at a time when others appear to be perfectly normal. From our own experience, using the new neutral red method as given in the first paper of this series,[7] we may add that histologic evidence of the

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

7. Covell, W. P., and O'Leary, James L.: Nerve Degeneration in Poliomyelitis: I. Vital Staining with Neutral Red Applied to Nerve Degeneration, Arch. Neurol. & Psychiat. **27**:518 (March) 1932.

degenerative processes may be found earlier in one portion of a fiber than in another, so that when changes are not observed in the segment of a particular fiber available for study, it does not mean that they are also absent in other parts of the same fiber.

In general, the following results are indicative of the average histologic appearance of the myelinated fibers at stages during the depression of the conducted action potential. They are based on the study of serial, 5 micron, longitudinal sections (osmic acid-stained) of the vagus nerves of cats killed at intervals postoperatively. Here, fibers of the different groups occur side by side in sufficient numbers to facilitate comparison.

At an early stage during the depression of the conducted action potential (for convenience, the period between twenty-four and forty-four hours), varicosity is not uncommon among fibers of the large, heavily myelinated and medium-sized, thinly-sheathed groups. Amplification of the incisures and widening at the nodes (Cajal[6]) are of infrequent occurrence. Consequently, while at this stage this observation is quantitatively of minor significance, its qualitative import is indicated by the fact that at a later stage these alterations are detected with increasing frequency in the more resistant fibers of the thickly-sheathed, large, myelinated group. Altered fibers are not as frequent among the fine, myelinated as among those of medium and large size. In them, change is confined to hypertrophy of the perinuclear cytoplasm of the Schwann's cells with constriction of the diameters of segments of the fibers. Since this appearance is also present, though to lesser degree, in comparable fibers of normal nerves, it should not receive undue emphasis as evidence of early degenerative change.

As degeneration progresses, fragmentary change becomes apparent in myelinated fibers of all sizes. The involvement is most frequently met with in the medium-sized, thinly-sheathed fiber group; but fragmented fibers of both the large somatic and fine autonomic are also seen. From seventy to ninety hours, many of the large, myelinated fibers, hitherto resistant to degenerative change, evince early fragmentation. Among these, the classic description of early degenerative change may be verified: occurrence of thinned, myelinic segments, widened nodes and amplified incisures. Also at this time, certain of the fine, myelinated fibers still retaining an intact myelin sheath (a significant number, table 2), stain less vigorously with osmic acid acid than their fellows.

To render the histologic changes easy of comparison, counts were made of a hundred members of each of the three groups of myelinated fibers which are responsible for components of the conducted nerve potential. Osmic acid, 5 micron, longitudinal sections of the vagus

nerve were used. Each counted fiber was placed in one of two groups: those intact throughout the segment available for study, and those fragmented. Earlier changes in the groups of large and medium-sized fibers, such as the occurrence of nodes and thinned myelinic segments, were disregarded. The ratio of fragmented to nonfragmented fibers in each of two groups was taken as an index of the average rapidity of degeneration in one as compared with the other.

Our primary interest concerned the correlation of the rate of change in the amplitudes of the components of the conducted nerve potential

TABLE 2.—*Ratio of Fragmented to Nonfragmented Myelinated Fibers of the Several Size Groups Responsible for Components of the Action Potential at Intervals Following Section of the Vagus Nerve*

		Ratio of Fragmented to Nonfragmented Fibers, Basis 100 Fibers					
		Large Thickly Myelinated†		Medium-Sized Thin Sheathed‡		Fine Myelinated§	
Hours Cut	Degree of Depression*	Fragmented	Nonfragmented	Fragmented	Nonfragmented	Fragmented	Nonfragmented
55	Usually relative depression in potentials corresponding to myelinated fibers: A, ++; B_1, +++; B_2, +; C, —	30	70	71	29	22	78
61	Usually relative depression: A, ++; B_1, abs.; B_2, +; C, —	47	53	77	23	28	72
68	Usually relative depression: A, abs.; B_1, abs.; B_2, ++; C, +	56	44	78	22	31	69
84	Usually abs. of myelinated potentials; C, +++	59	41	84	16	45	55
94	Abs. in all potentials	79	21	..	..	63	37

* The degree of depression in indicated by ++; the normal area of potential, —; absolute depression, abs.

† The fibers in this group had the following selected range: diameter, from 6.7 to 18.1 microns; sheath thickness, from 1.4 to 2.4 microns.

‡ The fibers in this group had the following selected range: diameter, from 4.8 to 6.5 microns; sheath thickness, from 0.43 to 0.85 microns.

§ The fibers in this group had the following selected range: diameter, from 1.4 to 3 microns; sheath thickness, from 0.4 to 0.65 microns

with the rate of morphologic change in the degenerating fibers. Therefore, stages from fifty-five to ninety-four hours were selected for the counts. After ninety hours, a very few functionally active fibers may still be present, but with the amplification used these never gave rise to a recognizable potential. Structurally intact, myelinated fibers of all sizes (in varying proportions) do persist after ninety hours; but the more rapid removal of débris in the fine autonomic fibers introduced an obvious inaccuracy into counts carried beyond this period.

The results of such counts are given in table 2. The ratios within the groups of large, thickly myelinated and fine, myelinated fibers indicate that the average rate of degeneration within the specified time limit is more rapid in the group of large fibers. When those for the large,

thickly myelinated and thinly-sheathed, medium-sized fibers are compared, the susceptibility to degeneration appears to be more marked among the medium-sized.

These contrasts are not easily made in somatic nerves because of the greater preponderance of the large, somatic fibers. For purposes of

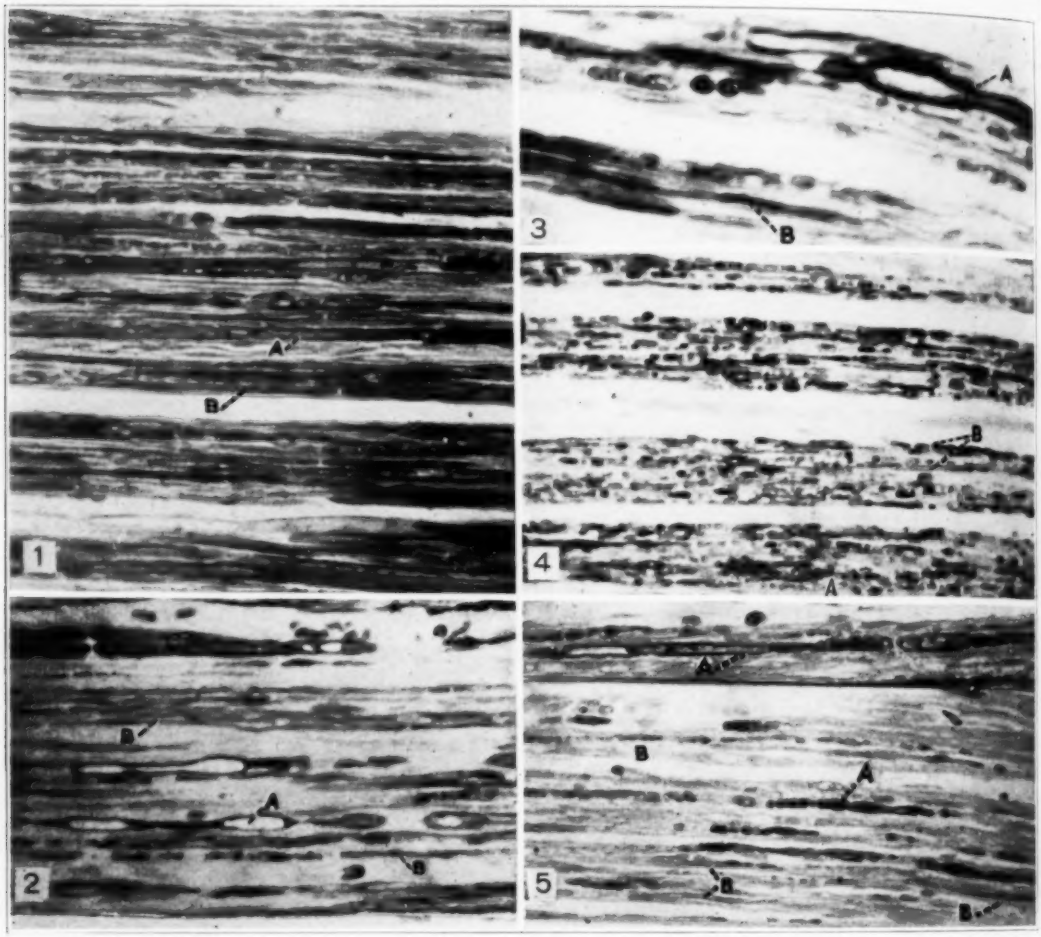

Fig. 2.—Photomicrographs of 5 micron longitudinal sections; osmic acid stain. *A* large, thickly myelinated fibers; *B*, fine, myelinated fibers; *1*, vagus cut fifty-five hours previously; *2*, cut sixty-eight hours; *3*, cut eighty-four hours; *4*, cut ninety-eight hours; *5*, cut one hundred and seventeen hours. The depression of the action potential at the stage corresponding to *1* is usually *A*, +; B_1, +++; B_2, +, and *C*, unaltered. Note the peristence of fine, myelinated fibers in the eighty-four, ninety-eight and hundred and seventeen hour nerves. Zeiss 8 mm., oc. × 15. Magnification (except *III*), 275 diameters; *III*, 540 diameters.

comparison with the ratios of fragmented to nonfragmented large fibers in the vagus nerve series, table 3 gives the results of counts of members of this group in typical somatic nerves at stages from sixty to ninety-six hours.

Average areas of the vagus nerve (osmic acid-stained, 5 micron, longitudinal sections) at stages from fifty-five to one hundred and seventeen hours are illustrated in the photomicrographs of figure 2. Comparison reveals the persistence of intact, fine myelinated fibers to a late stage.

In the vagus nerve, the relative resistance of myelinated fibers as compared with nonmyelinated was also studied. As early as fifty-five hours, certain of the nonmyelinated axons, a small number, had become granular and were fragmented in places. However, the majority

TABLE 3.—*Ratio of Fragmented to Nonfragmented Large, Thickly Myelinated Fibers at Intervals Following Section of Somatic Nerves*

Nerve	Hours Cut	Comment	Ratio of Fragmented to Nonfragmented Fibers, Basis 100 Fibers	
			Fragmented	Nonfragmented
Ulnar	60	Depression +++	44	56
Median	72	Depression abs.*	69	31
Sciatic	84	.....	81	19
Sciatic	96	.....	89	11

* Abs. indicates absolute depression.

appeared to persist intact to a late stage. Groups of them and single fibers, intact throughout their course but occasionally exhibiting slight varicosities, were observed among the granular fragmented remnants of the myelinated axons at the seventy-nine, ninety-two and one hundred and two hour stages. Figure 3 permits the comparison of average areas (Ranson's pyridine silver modification of the Cajal method) of the vagus nerve at the fifty-fifth and one hundred and second hours.

COMMENT

Functional studies made heretofore have not permitted a complete examination of the order of loss of function of the fiber groups in a nerve trunk. No method of grading the strength of stimulation necessary for such a purpose was available. This has been afforded through the development of the cathode-ray oscillograph as a recording mechanism and the establishment of a correlation between the form of the conducted action potential of a nerve trunk and its fiber composition. However, the literature affords some data pertinent to our problem.

Howell and Huber [8] found that, in dogs, somatic muscles failed to respond to nerve stimulation after four days of degeneration. As the *A* potential includes that of fibers responsible for the ordinary muscle

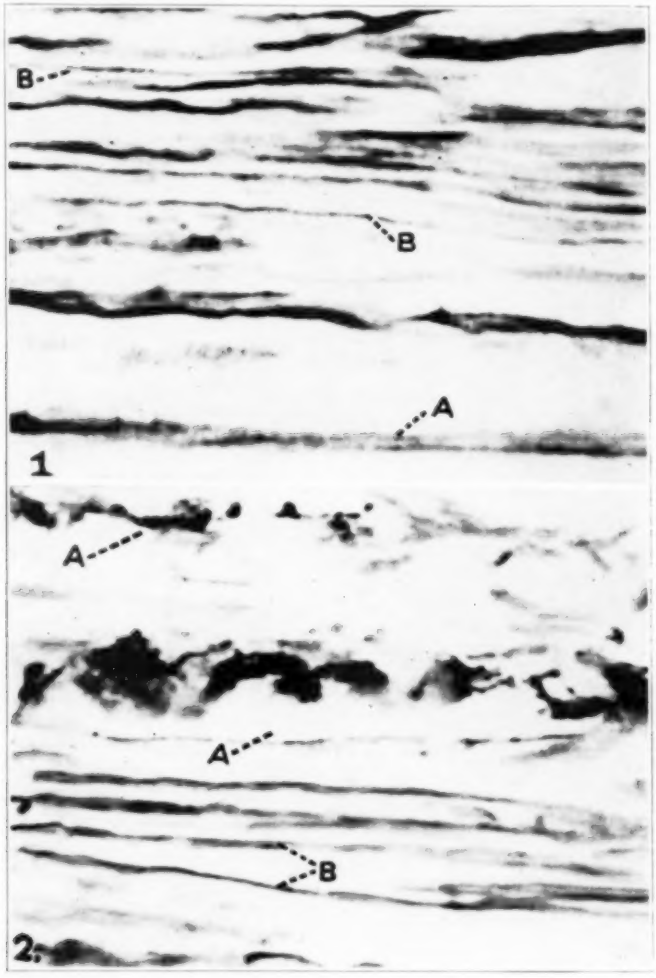

Fig. 3.—Photomicrograph of 5 micron longitudinal section; Cajal-Ranson silver method for axons. The vagi nerves were cut fifty-five (*1*) and one hundred and two (*2*) hours previously. Note the persistence of nonmyelinated axons at the late stage as compared with frankly degenerating myelinated ones. *A*, large myelinated fibers; *B*, nonmyelinated fibers. Zeiss 3 mm., oc. × 15. Magnification, 1,600 diameters.

8. Howell, W. H., and Huber, G. C.: Physiological, Histological and Clinical Study of the Degeneration and Regeneration in Peripheral Nerve Fibers After Severance of Their Connections with the Nerve Centers, J. Physiol. **13**:335, 1892.

twitch, we have evidence of fair agreement between their results and our own. Their time is slightly longer, but it is to be remembered that the species of animal studied was different, and also it is possible that a very few active fibers might still be present in the cat at the end of three days without affording a recognizable potential at the amplification employed.

It is well known that in mammals after from three to four days stimulation of the peripheral end of the severed vagus nerve fails to induce cardio-inhibitory effects. It has been established by Heinbecker [9] that in the turtle the unmyelinated fibers of the vagus are responsible for cardiac slowing. It is highly probable that the same fiber type is concerned with this function in the dog. Assuming this, there is again good agreement with our present results and functional studies. No recognizable potential was elicited from unmyelinated fibers after ninety hours.

It is of interest to note that the absolutely refractory period was again the most sensitive criterion of change in the nerve's physiologic state. An increase of its value over the normal has been found by us to be a first index of depression following the application of many of the ordinary substances known to be nerve depressants. The ease and exactitude with which this can be determined warrants advocating its wider application in pathologic studies.

The results of this investigation also afford evidence of a differential susceptibility of nerve fibers to the processes of wallerian degeneration. The decrescence of function in the various groups parallels in a fair way other knowledge concerning their physiologic properties. The fibers of slower orders (high threshold, slow conduction rate, and long refractory period), namely, the fine, myelinated and nonmyelinated in visceral nerves, retain their capacity to conduct the nerve impulse over a longer period than do the fibers of faster order, namely, those of the large, thickly myelinated and medium-sized, thinly-sheathed varieties.

Other students of nerve degeneration have adduced histologic evidence that the fibers of one or another of the groups considered pass through the stages of wallerian degeneration more rapidly than do those of the others.

Van Gehuchten and Molhant [10] examined the vagus nerves of rabbits at intervals following the rupture of the intracranial filaments. They determined changes as early as forty hours in large, myelinated fibers

9. Heinbecker, P.: The Effect of Fibers of Specific Types in the Vagus and Sympathetic Nerves on the Sinus and Atrium of the Turtle and Frog Heart, Am. J. Physiol. **98**:220, 1931.

10. Van Gehuchten, A., and Molhant, M.: Les lois de la dégénérescence wallerienne directe, Névraxe **11**:75, 1910.

(osmic acid method). In successively later stages, studied by the Marchi method, black globules indicating the decomposition of myelin (Mott and Halliburton [11]) appeared in the fine, myelinated fibers before they did in the large. They interpreted this to mean that the evolution of secondary degeneration was more rapid in the fine fibers. Their interpretation is undoubtedly correct so far as the changes they described were concerned, but physiologic and histologic evidence indicates that the average rapidity of early degenerative change is greater in the large than in the fine fibers.

Cajal [12] commented on the slower degeneration of "sympathetic or nonmedullated" fibers as compared with myelinated ones as follows: "These are the most resistant of all, remaining almost normal forty-eight and fifty-six hours after the section. Finally, that is from the fourth to the seventh day, they too undergo granular degeneration. . . ." Ranson [13] described nonmedullated afferent fibers in the spinal nerves. In a later paper [14] he stated that in these afferent spinal fibers degenerative changes appear early, but confirmed Cajal's results regarding the late degeneration of other nonmyelinated fibers. Our own results, both histologic and physiologic, are in agreement with those of Cajal and also those of Ranson [13] as far as this latter group is concerned.

SUMMARY

The vagus, cervical sympathetic and various somatic nerves were severed aseptically in fifteen young adult cats and one monkey. The animals were killed at intervals from twelve to one hundred and seventeen hours and the distal segments examined by physiologic and histologic methods. For the functional study, the cathode-ray oscillograph was employed to record the conducted action potentials of the severed nerves and their controls. For microscopic examination, chief reliance was placed on the appearance of fragmentation in the medullary sheaths, as evidenced in osmic acid-stained preparations. Ranson's pyridine-silver modification of the Cajal method was used to check the relative rates of degeneration in myelinated and nonmyelinated fibers.

Results of the physiologic study showed: 1. Increase in the absolutely refractory period may be detected as early as twelve hours after section. 2. Significant reduction in potential area was usually not apparent before thirty-six hours. 3. The fiber groups of somatic and

11. Mott, F. W., and Halliburton, R.: The Chemistry of Nerve Degeneration, Phil. Tr. Roy. Soc. London **194**:437, 1902.

12. Cajal (footnote 6, p. 105).

13. Ranson, S. W.: Nonmedullated Nerve Fibers in the Spinal Nerves, Am. J. Anat. **12**:67, 1911.

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

visceral nerves characterized by different physiologic properties lose their action potentials in sequence. The potential from visceral afferents disappears first at from fifty to seventy hours; the potential from somatic motor and sensory fibers, five to ten hours later; then the potential from myelinated autonomics, and finally, the potential from unmyelinated fibers. A potential from unmyelinated fibers has not been elicited later than ninety hours postoperatively.

In differential counts of three groups of myelinated fibers (large fibers, selected range, diameter from 6.7 to 18.1 microns; sheath thickness, from 1.4 to 2.4 microns; medium-sized, selected range, diameter from 4.8 to 6.5 microns, sheath thickness, from 0.43 to 0.85 micron: fine, selected range, diameter from 1.4 to 3.0 microns, sheath thickness, from 0.4 to 0.65 micron), fragmentation was set as an arbitrary criterion of degeneration. Those fibers not exhibiting fragmentation in the portion available for study in a 5 micron longitudinal section, stained with osmic acid, were counted in one group; those exhibiting fragmentation in at least one place, in another. The comparative values (table 2) indicate that fragmentation occurs earlier on the average in the medium-sized, relatively thin-sheathed group, next in the large, myelinated fibers, and finally in the smallest, myelinated ones. Numerous nonfragmented unmyelinated axons persist at a stage when in osmic acid stained preparations the sheaths of almost all myelinated fibers appear to be fragmented.

THE SEX RATIO IN MIGRAINE

WILLIAM ALLAN, M.D.
CHARLOTTE, N. C.

The frequency of the occurrence of migraine in women as compared with men is a matter of interest because of the relation of this disproportionate sex ratio to the inheritance of migraine.[1] Present knowledge of this sex ratio is derived from the reports of clinical cases, as shown in table 1, and shows a preponderance of women over men.

On the other hand, Gowers [2] said, "The preponderance of females has been greatly exaggerated," and Crookshank [3] has more recently said that "Perhaps men suffer more frequently from true migraine than do women."

This preponderance of women in clinical reports led Jens Smith,[4] while concluding that migraine was inherited directly as a dominant trait, at the same time to conclude that it must in some way be sex-linked. He offered as evidence the statement that migraine most frequently descends from mother to daughter, next in frequency from mother to son, then from father to daughter, and least in frequency from father to son. My observations on this phase of the question, as shown in table 2, fail to confirm Smith's statement, for women have given me the history of headaches coming from father or mother, or both, in relatively the same proportion as men.

It is probably unnecessary to point out that if a sex-linked dominant trait is carried on the x-chromosomes of either the male or female, such a trait will predominate in the female descendants only when a dominant father is mated to a normal mother or a mother heterozygous dominant for such a trait; in both of these incidences the female descendants showing the trait would give a history of deriving it from either father alone or both parents, but not from the mother.

As may be seen from tables 5 and 6, whether a dominant sex-linked trait is carried by mother or father, half the male descendants showing the trait would give a positive maternal history and half would give a positive history in both parents, but none would give a positive paternal

Submitted for publication, June 25, 1931.

1. Allan, W.: The Inheritance of Migraine, Arch. Int. Med. **42**:590 (Oct.) 1928.

2. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, Philadelphia, P. Blakiston's Son & Company, 1893, p. 836.

3. Crookshank, F. G.: Migraine and Other Common Neuroses, London, Kegan Paul, Trench, Trubner & Co., Ltd. 1926, p. 73.

4. Smith, Jens: Bibliot. f. læger **114**:310 (Aug.) 1922.

history alone, while the female descendants showing such a trait would give a positive parental history in the following ratio: Three would give a positive maternal history, four would give a positive history in both parents, and two would give a positive paternal history. Thus, if

TABLE 1.—*Sex Ratio of Migraine in Reports of Clinical Cases*

	Total Number	Women	Men	Ratio F. M.
Symonds: Gulstonian Lectures, M. Times & Gaz. **16:** 498, 1858	90	76	14	5.4 : 1
Liveing: Megrin, Sick Headache and Allied Disorders, London, J. & A. Churchill, 1873	93	52	41	1.3 : 1
Wilson: Nervous Diseases, Philadelphia, Lea Brothers & Company, 1895, p. 939	..	..	..	3.5 : 1
Kovalevsky: La migraine et son traitement, Paris, Vigot frères, 1902, p. 18	..	..	..	2.5 : 1
Moebius: Die Migräne, Vienna, A. Hölder, 1903, p. 15	130	78	52	1.5 : 1
Dana: Nervous Diseases and Psychiatry, Philadelphia, William Wood & Company, 1904, p. 181	..	..	..	3.0 : 1
Flatau: Die Migräne, Berlin, Julius Springer, 1912	..	..	..	1.7 : 1
Laing: M. Clin. North America **11:** 49, 1927	145	116	29	4.1 : 1
Smith: Bibliot. f. læger **114:** 310 (Aug.) 1922	733	533	200	2.7 : 1
Reiley: Headache, Philadelphia, P. Blakiston's Son & Company, 1926, p. 228	..	..	..	4.0 : 1
Bramwell: Brit. M. J. **2:** 765, 1926	61	43	18	2.4 : 1
Allan	678	478	200	2.4 : 1

TABLE 2.—*Sex Ratio of the Inheritance of Migraine*

	Men		Women		Sex Ratio
	Number	Per Cent	Number	Per Cent	M. F.
Father had headache	29	19	72	18	1 : 2.5
Mother had headache	74	49	209	53	1 : 2.8
Both had headache	34	22	85	22	1 : 2.5
Neither had headache	16	10	26	7	1 : 1.6
Total	153		392		1 : 2.5
	545				

migraine should pass most frequently from mother to daughter, it would not correspond with a unit dominant sex-linked hereditary character.

There are a number of possible explanations for the discrepancy between the sexes: 1. It may be that authors reporting on the incidence of migraine see two or three times as many women as men; however, in a tabulation of 6,000 consecutive case histories of all sorts, I [5] found

5. Allan, W.: Is Hypertension Acquired or Inherited? South. Med. & Surg. **92:**491, 1930.

that I see, year in and year out, approximately equal numbers of men and women, so that this is not the reason that women outnumber men among my patients with headache.

2. Possibly many types of headache in women have been included that were not true migraine. Considering flittering scotoma to be pathognomonic of migraine, I have analyzed 402 case histories in which the presence or absence of flittering scotoma was definitely noted. Of the 122 men, 74, or 60 per cent, had flittering scotoma, and of 280 women, 127, or 45 per cent, had flittering scotoma. However, if enough

TABLE 3.—*Recessive Gene (r) Carried on X-Chromosomes of the Female* *

1 *rr* × DY = Dr *rY* Dr *rY*	
2 Dr × DY = DD DY Dr *rY*	Male : female = 6 : 3
(3 DD × DY)	
4 *rr* × *rY* = *rr* *rY* *rr* *rY*	
5 Dr × *rY* = Dr DY *rr* *rY*	
6 DD × *rY* = Dr DY Dr DY	

* D indicates dominant; r, recessive. The similar letters represent the two x-chromosomes of the female, and the letter associated with Y, the x-chromosome of the male. Y always denotes a male. Those with the trait manifest are in italics.

TABLE 4.—*Recessive Gene (r) Carried on X-Chromosome of the Male*

1 DD × rY = Dr DY Dr DY	
2 Dr × rY = Dr DY *rr* *rY*	Male : female = 6 : 3
3 rr × rY = *rr* *rY* *rr* *rY*	
(4 DD × DY)	
5 Dr × DY = DD DY Dr *rY*	
6 rr × DY = Dr *rY* Dr *rY*	

histories of women without scotoma are eliminated to make the percentage of scotoma in the two sexes equal, there are still almost twice as many women as men, so that the inclusion of nonmigrainous headaches in women is not the answer to this problem.

3. Although the inheritance of migraine may be the same in men and women, clinical headache may not develop at all in a certain proportion of men—incomplete dominance. I know of nothing that would support this explanation except that of the small number of persons in whom migraine develops as late as the fourth decade, there are more men than women.

4. If migraine is inherited as a unit character and sex-linked, it must be either dominant or recessive, and carried on the x-chromosomes of either the male or the female. Sex-linked recessive traits [6] appear in more male than female descendants, as may be seen in tables 3 and 4.

6. Morgan, T. H.: The Physical Basis of Heredity, Philadelphia, J. B. Lippincott Company, 1919, p. 168.

Sex-linked dominant traits, whether carried on the male or female x-chromosomes, appear in more female than male descendants, as illustrated in tables 5 and 6, so that it is necessary to determine the actual relative incidence of migraine in the two sexes in the general population.

TABLE 5.—*Dominant Gene Carried on X-Chromosomes of the Female*

	Parenteral History
1 *DD* × rY = *Dr DY Dr DY*	2 males = maternal : 2 females = maternal
2 Dr × rY = *Dr DY* rr rY	1 male = maternal : 1 female = maternal
(3 rr × rY)	
4 *DD* × *DY* = *DD DY DD DY*	2 males = both parents : 2 females = both parents
5 *Dr* × *DY* = *DD DY Dr* rY	1 male = both parents : 2 females = both parents
6 rr × *DY* = *Dr* rY *Dr* rY	2 females = paternal
Male : Female = 6 : 9	Males = 3 maternal, 3 both parents
	Females = 3 maternal, 4 both parents, 2 paternal

TABLE 6.—*Dominant Gene Carried on X-Chromosome of the Male*

	Parenteral History
1 rr × *Dy* = *Dr* rY *Dr* rY	2 females = paternal
2 *Dr* × *DY* = *DD DY Dr* rY	1 male = both parents : 2 females = both parents
3 *DD* × *DY* = *DD DY DD DY*	2 males = both parents : 2 females = both parents
(4 rr × rY)	
5 *Dr* × rY = *Dr DY* rr rY	1 male = maternal : 1 female = maternal
6 *DD* × rY = *Dr DY Dr DY*	2 males = maternal : 2 females = maternal
Male : female = 6 : 9	Males = 3 maternal, 3 both parents
	Females = 3 maternal, 4 both parents, 2 paternal

* D indicates dominant; r, recessive. The similar letters represent the two x-chromosomes of the female, and the letter associated with Y, the x-chromosome of the male. Y always denotes a male. Those with the trait manifest are in italics.

TABLE 7.—*Duration of Headaches*

	Men		Women	
	Number	Per Cent	Number	Per Cent
One day or less	121	87.0	222	67.0
Two days	12	8.6	64	19.4
Three days	6	4.4	35	10.6
Over three days	..	...	10	3.0
	139		331	

TABLE 8.—*Frequency of Nausea and Vomiting*

	Men		Women	
	Number	Per Cent	Number	Per Cent
With nausea	92	63	238	70
Without nausea	54	37	102	30
With vomiting	78	53	209	61
Without vomiting	68	47	131	39

EXPERIMENTAL DATA

As occupation [7] plays no part in the incidence of migraine in either sex, the members of the Mecklenburg County Medical Society and their wives were selected for investigation of the incidence of migraine. This group of men and women, because of intelligence and more or less familiarity with the subject, would give more accurate histories and would submit to more persistent quizzing than any group I could reach; they constitute a fair random sample of the general white population of North Carolina.

Among 103 men, 56, or 54 per cent, gave a history of periodic headaches that could be clinically classified as definite migraine; 90 per cent of these gave a positive parental history; 48 per cent had both hemicrania and flittering scotoma, and in 73 per cent the headaches had started before the age of 21. In addition, 13 had headaches that were too infrequent or too atypical to be definitely recognized as periodic migraine; but even in this group there was a positive parental history of migraine in 91 per cent. Among the 34 men without headache, there was a positive parental history in 29 per cent.

Among the 92 wives, there were 50, or 53 per cent, with definite clinical migraine, 90 per cent having a positive parental history, 55 per cent having hemicrania and 40 per cent flittering scotoma, with the onset before the age of 21 in 85 per cent. In addition, there were 7 women with headaches too infrequent or too atypical to be recognized as migraine. A comparison of the frequency of typical migraine, atypical headaches and no headaches in the 103 physicians as compared with the 92 wives shows that the frequency of migraine is the same in the two sexes.

While the frequency of migraine in men and women seems to be the same, for anatomic and physiologic reasons migraine is more often a more severe malady in women than in men, as shown by the greater duration of the headaches and the somewhat greater frequency of nausea and vomiting in women.

CONCLUSIONS

The incidence of migraine is the same in men as in women, but, clinically, one sees more women than men with migraine, because the headache is more often severer in women.

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7. Allan, W.: The Relation of Occupation to Migraine, J. Nerv. & Ment. Dis. **66**:131, 1927.

Clinical Notes

ENCAPSULATED BRAIN HEMORRHAGES

A Study of Their Frequency and Pathology

G. Wilse Robinson, Jr., M.D., Kansas City, Mo.

While preparing a case of encapsulated brain hemorrhage for presentation at a meeting of the Philadelphia Neurological Society, it was found that in the records of the neuropathology laboratory of the Philadelphia General Hospital there were only two cases of this character in about four thousand cases studied in the laboratory. Dr. W. G. Spiller kindly allowed me access to his collection, in which were three similar cases in about eight hundred. The small incidence led me to consider that they should be reported.

A study of the literature of these cases seems to show that a brain hemorrhage, even when rather extensive, does not cause sudden death and that even recovery may occur, provided that the hemorrhage is either walled off, if large, or absorbed, if small. To my knowledge, however, only two such cases have been reported in English. Spiller [1] reported a case in 1906 among thirteen cases of extensive brain hemorrhage, with death and necropsy. This case is being used in the present series. Douglas,[2] in 1925, reported a hemorrhage of four years' duration, which was encapsulated and cystic. I shall discuss this case in more detail later.

The duration of life after hemorrhage into the brain is not known exactly. Spiller, in thirteen cases, found that the patients survived for from five hours to two months after a hemorrhage into the brain, and concluded that rapid death does not follow a cerebral hemorrhage. Thomas,[3] Spillsbury [4] and Maloney,[5] from separate series of cases, concluded that cerebral hemorrhage is not a cause of sudden death, and Oppenheim,[6] while agreeing with them, stated that only medullary hemorrhage will cause sudden death.

Cadwalader [7] found that cerebral hemorrhages are apt to be large. Of twenty-four cases reported in 1911, only four measured less than 4 cm. in their broadest diameter. He concluded that large hemorrhages are always fatal, and that it is probable that all hemorrhages may be fatal. He also did not believe that hemor-

Submitted for publication, Aug. 24, 1931.

1. Spiller, W. G.: The Duration of Life After Extensive Hemorrhage of the Brain, J. A. M. A. **51**:2101 (Dec. 19) 1908.

2. Douglas, R. G.: A Case with an Old and a Recent Hemorrhage, Canad. M. A. J. **15**:638, 1925.

3. Thomas, H. M., in Osler: System of Medicine, Philadelphia, Lea & Febiger, 1915, vol. 5, p. 452.

4. Spillsbury, B. H.: Sudden Death, Practitioner **98**:132, 1917.

5. Maloney, M. J.: Sudden Death, Dublin J. M. Sc., February, 1921, p. 60.

6. Oppenheim, H.: Lehrbuch der Nervenkrankenheiten, ed. 7, Berlin, S. Karger, 1923, p. 1238.

7. Cadwalader, W. B.: A Comparison of the Onset and the Character of the Apoplexy Caused by Cerebral Hemorrhage and by Vascular Occlusion, J. A. M. A. **62**:1381 (May 2) 1914.

rhages will cause sudden death. Winkelman and Eckel,[8] in an analysis of thirty cases of proved hemorrhages, in which the times of onset and death were definitely known, believed that cerebral hemorrhage does not cause immediate death, that is, in less than one hour, even in cases of hemorrhage within the pons or of rupture into the ventricles.

Kron and Mintz[9] reported an operation on a patient with cerebellar hemorrhage seventeen days after the onset of symptoms, with practically complete recovery. The hemorrhage was the size of a bird's egg, and invaded the right side of the cerebellum near the midline to a depth of 6.75 cm. It was not encapsulated.

The pathologic process is similar to that of hemorrhage in other parts of the body, plus a characteristic neurologic reaction. Oppenheim[6] stated that apoplectic cysts may be found three or four weeks after a hemorrhage has occurred. The adjacent cerebral substance forms by proliferation of the glia and connective tissue a sort of capsule around the hemorrhagic focus. The contents of the capsule are gradually absorbed, until there remains only a cavity filled with serous fluid. It is seldom that complete cicatrization takes place.

Buzzard and Greenfield[10] stated that early the seat of the hemorrhage is occupied by a red clot, which is easily separated from the surrounding tissues. These tissues are infiltrated and softer than usual. Later, the clot and the walls undergo changes. The clot shrinks, remaining red in the center and growing yellow at the periphery. After a lapse of time, the coagulum becomes completely absorbed, and its place is taken either by proliferated scar tissue or by a quantity of more or less blood-stained fluid. Changes in the wall are taking place during this time, namely, the destruction of the nerve elements and the proliferation of the neurological tissue. The newly formed glial substance either forms the lining membrane of the cavity or binds the walls together. The final results may be either a large single cavity, a multilocular cavity or a linear scar. These relics can scarcely be distinguished from other lesions of similar antiquity.

This view—that vascular lesions of the brain substance, when of considerable age, are indistinguishable from each other—is held by most workers in this subject. Douglas thought that the finding of blood pigment in some quantity around a focus proved that the lesion was a hemorrhage. In his case, the patient had had a vascular insult to the brain from which he had recovered; four years later, he died from a second insult. At necropsy a fresh hemorrhage was found in the left internal capsule, which had ruptured into the ventricle, and was the immediate cause of death. On the right side was the older lesion, which had occurred four years before. This consisted of a cyst, filled with clear yellow fluid, surrounded by a fibrous membrane, outside of which was an area of yellow pigmentation in the surrounding brain; microscopically, this proved to be blood pigment.

REPORT OF CASES

Case 1.—Spiller's case, reported in the series in 1906, showed clinically a right spastic hemiplegia and aphasia. A month and a half after the sudden onset, an operation was performed, and a left subdural hemorrhage was found. The patient died two weeks later, and a hemorrhage, measuring 7 by 2.5 cm., was found in the

8. Winkelman, N. W., and Eckel, J. L.: Extensive Brain Hemorrhages, J. Nerv. & Ment. Dis. **61**:593, 1925.

9. Kron, I., and Mintz, W. G.: Kleinhirnblutung geheilt durch Operation, Deutsche med. Wchnschr. **53**:1054 (June 17) 1927.

10. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Nervous System, London, Constable & Co., Ltd., 1921, p. 118.

left ventricular nucleus and internal capsule. The clot appeared to be of long duration and was partly encapsulated.

CASE 2.—F. S. was admitted to the University Hospital on Jan. 24, 1900, with a history that on Sept. 27, 1899, paralysis of the right side of the face, deafness of the right ear and pain in the right eye had developed. On Dec. 21, 1899, he had an apoplectic seizure of the right side. A month later, he was admitted to the hospital in a semiconscious condition, with a central paralysis of the right side of the face, deafness of the right ear and motor aphasia. Sensation of the skin was normal. Death occurred six weeks after the onset. Necropsy revealed a small hemorrhage, measuring 1.5 by 1 cm., in the left optic thalamus and internal capsule; it was firmly encapsulated and walled off from the normal brain substance.

CASE 3.—W. E., aged 54, suddenly became unconscious for an hour in August, 1917. The right leg was paralyzed. Five months later, speech became affected, and he could not speak properly. He was admitted to the University Hospital, on Dr. Spiller's service, where he showed poor mentality and rather contradictory physical signs: the tongue tended to deviate to the left, but the right side of the face was weak; the reflexes of the upper extremities were normal, but the left patellar reflex was exaggerated; there was also a Babinski sign on the right, but not on the left. The patient died on Aug. 16, 1918. Necropsy revealed a small encapsulated hemorrhage in the right optic thalamus and internal capsule, with an area of softening in the left occipital lobe.

Comment.—These three patients from the Spiller collection of cases lived from two months to one year after the acute onset; one of the patients of the Philadelphia General Hospital series lived forty-six days, the other fifty-three days.

CASE 4.—A white man, aged 66, while fishing had a stroke that affected the whole left side. Twenty-three days later, he was admitted to the neurologic service of Dr. J. W. McConnell. Examination revealed a typical spastic left hemiplegia. The patient died on June 2, forty-six days after the onset of the trouble. A diagnosis of right cerebral thrombosis and chronic myocarditis had been made. The necropsy revealed myocardial hypertrophy and degeneration, with secondary coronary sclerosis. There was congestion of the liver and spleen, with chronic glomerular nephritis. The brain was normal in size, shape and weight. The hemispheres presented a moderate edema; there were fibrosis of the membranes and a marked arteriosclerosis. Section of the brain in the horizontal plane revealed a hemorrhage in the right basal ganglion area; it was roughly oval and measured 5.5 by 2.5 cm.; it had destroyed the posterior portion of the internal capsule, the lenticular nucleus, the external capsule and the island of Reil and had invaded the anterior portion of the internal capsule. It was older than the usual hemorrhage, as it was surrounded by a membrane and was apparently becoming organized. The gross diagnosis was arteriosclerosis and encapsulated cerebral hemorrhage.

CASE 5.—The patient was admitted to the Philadelphia General Hospital with tabes, in 1916. On Nov. 23, 1923, he had a rapidly progressing right hemiplegia; he died on Jan. 15, 1924. Autopsy revealed a hemorrhage into the left lenticular region, 1.5 by 2 cm. wide and 6 cm. long, with a well marked capsule.

Histologic Studies.—Microscopically, these foci presented the following picture: The center of the lesion consisted of a disintegrating blood clot, at the periphery, in which were pigment-laden phagocytic cells of the microglial or gitter cell type. Immediately around the clot was a fairly dense network of fibrous tissue, which was being laid down in an effort to wall off the hemorrhagic focus from the rest of the brain. That this was fibrous tissue and not glial tissue was shown by differential stains (van Gieson); also, the fibrous tissue contained numerous young fibroblasts which were in the process of proliferation. The area was rather nar-

row, but extended around the entire clot. In the meshes of the fibrous tissue were also many pigment-laden phagocytic cells, these cells were larger and contained more pigment in the inner portion than in the outer, while in the outer margin were many lipoid-containing cells of the same phagocytic type.

The third concentric layer consisted of a softened area immediately around the fibrous capsule, in which were many closely packed gitter cells containing lipoid and some containing blood pigment. The perivascular spaces of the vessels contained numerous gitter cells. Around this area, which was not sharply defined, was a variable width of brain tissue showing status spongiosus. The Virchow-Robin spaces of the vessels contained a cellular exudate, many of the cells being naked nuclei, in appearance not unlike small lymphocytes.

The glial reaction merited special consideration, as there was a rather marked macroglial reaction in this region. The glia cells were more numerous than normal and were uniformly scattered throughout the fibrous tissue network and in the area beyond.

COMMENT

There are two points of interest in these cases, first, the clinical aspect, and, second, the pathologic reactions. From the clinical standpoint, it would seem that brain hemorrhage is a fatal condition. The five patients in the cases reported all died, even though the reaction of the brain was sufficient to wall off the hemorrhagic lesions to a greater or less degree. This view is borne out further by the scarcity of such cases in the literature and in pathologic laboratories. If this type of case were of frequent occurrence more cases would be found. I therefore think that while brain hemorrhages are never immediately fatal, the patients die in a variable length of time. I therefore agree with the opinion of Cushing, expressed many years ago, that when feasible these hemorrhages should be opened and drained at the earliest opportunity.

Pathologically, while the tissues of the brain make an effort to wall off hemorrhagic lesions, this is not usually successful. The reaction is by both fibrous tissue and glial elements, and is not complete after six weeks.

CONCLUSIONS

1. The elements of the brain react to wall off pathologic foci.

2. Brain hemorrhages are almost invariably fatal, even though a pathologic reaction has taken place.

THE PULSE CURVE IN A CASE OF PROGRESSIVE MUSCULAR DYSTROPHY

WALTER M. KRAUS, M.D., NEW YORK

The demonstration of abnormalities of the pulse rate in progressive muscular dystrophy is an added diagnostic point in doubtful cases. What follows emphasizes this. Goodhart and Globus [1] showed in 1918 and Globus [2] in 1923 that the heart

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1. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophies, with a Report of Changes in Cardiac Muscle in Two Cases, Neurol. Bull. **1**:386, 1918.

2. Globus, J. H.: The Pathologic Findings in the Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59 (Jan.) 1923.

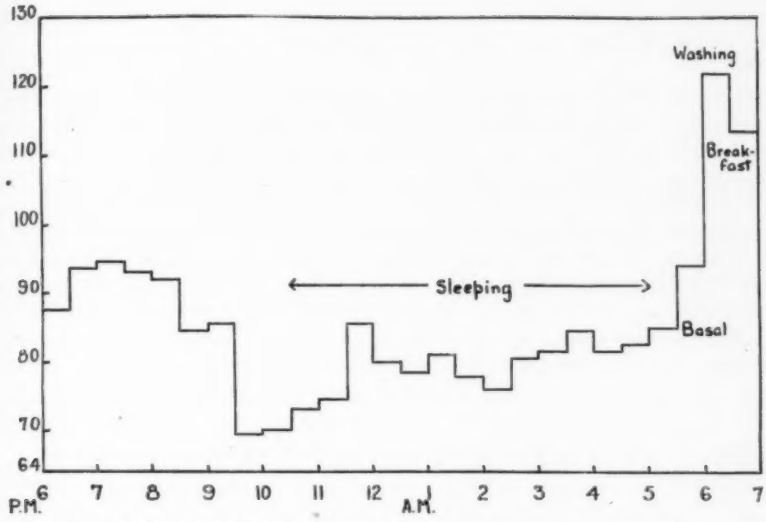

Fig. 1.—Graphic record of the heart rate of a patient with progressive muscular dystrophy (Boas,[5] 1931).

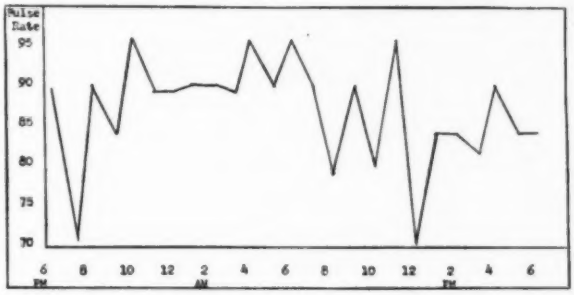

Fig. 2.—Graphic record of the heart rate of my patient with progressive muscular dystrophy, May 11 and 12, 1931.

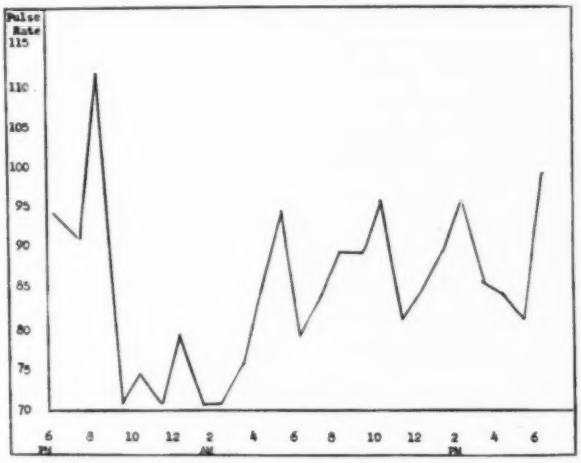

Fig. 3.—Graphic record, June 18 and 19, 1931, of the heart rate of same patient whose rate is given in figure 2.

muscle is diseased in muscular dystrophy. In 1929, Boas [3] published pulse curves during sleep, cardiotachometrically obtained, and demonstrated the great drop that normally occurs. In 1928, Boas [4] described the cardiotachometer, an instrument that can count automatically all of the pulse beats for indefinite periods of time. In 1931, Boas [5] published reports of seven cases of muscular dystrophy in which the normal drop during sleep was absent. It is therefore not unexpected to find such curves as are here given. Figure 1 is from one of Boas' cases; figures 2 and 3, from a case observed by me on the neurologic wards at Bellevue Hospital (service of Dr. Foster Kennedy). The pulse was taken at hourly intervals and not by the more exact method of cardiotachometry. Nevertheless, the curves demonstrate fully the absence of the normal drop in pulse rate during sleep.

The significance of this abnormality is not clear beyond indicating weakness of the heart muscles. As a result, there is a demand for more frequent contractions.

Further records of these relatively rare cases are desirable.

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3. Boas, E. P., and Weiss, M. M.: The Heart Rate During Sleep as Determined by the Cardiotachometer: Its Clinical Significance, J. A. M. A. **92**:2162 (June 29) 1929.

4. Boas, E. P.: The Cardiotachometer, an Instrument to Count the Totality of Heart Beats Over Long Periods of Time, Arch. Int. Med. **41**:403 (March) 1928.

5. Boas, E. P., and Lowenburg, H.: The Heart Rate in Progressive Muscular Dystrophy; Studies with the Cardiotachometer, Arch. Int. Med. **47**:376 (March) 1931.

SPECIAL ARTICLE

THE DIAGNOSIS AND TREATMENT OF TUMORS OF THE BRAIN

REVIEW OF THE SYMPOSIUM AT THE FIRST INTERNATIONAL NEUROLOGICAL CONGRESS

FRANCIS C. GRANT, M.D.
PHILADELPHIA

The papers presented on the opening morning of the International Neurological Congress at Bern dealt with three phases of the problem of tumors of the brain. In the first four communications certain aspects of the clinical neurologic symptoms of these lesions were considered. In the second group of papers the pathology of tumors of the brain was discussed, together with the variations in position, rapidity of growth and possibilities for complete extirpation without the recurrence noted in different types of tumors. Proper evaluation of these facts has an important bearing on preoperative prognosis and operative procedure. Lastly, mechanical methods of localization, by roentgen changes in the skull produced by the tumor, puncture of the brain and the injection of air or arterial encephalography were outlined, and the usefulness of each method was discussed. In this way the problems that present themselves in an attack on an intracranial tumor were taken up in logical order and considered in the same fashion that the case frequently demands when the neurologist or neurosurgeon studies a patient.

In his introductory comments, Sir James Purves-Stewart reviewed the mechanisms whereby a progressively expanding tumor affects the brain and produces symptoms. The clinical evidence of the presence of such a lesion results from pressure on and displacement of adjacent fiber tracts rather than from actual destruction of nerve elements by the tumor. But the most important factor in the causation of symptoms is the interference by the tumor with the circulation of the blood and the cerebrospinal fluid in contiguous areas. As the tumor increases in size, adjacent blood vessels are compressed and about the periphery of the lesion a zone of venous engorgement is produced with consequent irritative phenomena. As the tumor expands still farther, nearby capillaries are obliterated, anemia of the surrounding tissue occurs, and paralytic clinical symptoms result. As the lesion progresses, therefore, it produces an increasingly large paralytic zone surrounded by a still wider zone of irritation.

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Certain tumors, even though they are situated in or near active cortical areas, may give astonishingly little evidence of their presence. In all probability this is due to the small size of the lesion or to its slow growth, so that the surrounding brain is subjected gradually to circulatory disturbances, and has opportunity to adjust itself to them. Furthermore, the varying rate of the onset of circulatory disturbances may explain why similarly placed tumors produce widely different manifestations. Lesions producing a sudden intracranial pressure give much more widespread symptoms than do those accompanied by a more gradually appearing tension. For example, following severe cranial trauma delirium results, but in acute internal hydrocephalus merely drowsiness, while in chronic pressure due to a tumor, mental dulness only is observed. In cases of excessively slow development of pressure, as in infantile hydrocephalus, no mental change can be noted. But even in cases of chronic pressure, as in a tumor with slowly developing hydrocephalus, if for any reason a sudden blockage occurs, the symptoms may emerge rapidly from the latent to the active stage.

Broadly speaking, the general symptoms of tumor are due rather to interference with the circulation of the cerebrospinal fluid than to the presence of the foreign body itself. These general symptoms may exist regardless of the site of the tumor. Local symptoms vary with the site and size of the tumor and its effect on the circulation of the blood and the spinal fluid in adjacent structures.

Following these introductory comments on the symptomatology of tumors of the brain in general, Vincent, Ayala, and Kennedy discussed the clinical picture accompanying a neoplasm in the midline above the tentorium, in the subtentorial space and in the frontal and temporosphenoidal areas of the cerebral hemispheres.

Vincent is of the opinion that although tumors obstructing the aqueduct of Sylvius are relatively uncommon, they present a real problem in diagnosis which is often difficult to solve. Failure to find a proper solution results only too often in disaster for the patient and surgeon.

In certain of these tumors, the clinical signs that accompany them may give some clue to their position. This is particularly true if the optic chiasm, the pineal body, the quadrigeminal plate or the cerebellar lobes are involved. In the majority of cases, however, no signs of any value in localization can be noted. Evidences of intracranial pressure alone are present. Ventriculography or encephalography must then be used to solve the problem. Even after the injection of air, only the position of the lesion and not its type, whether a tumor or an inflammatory reaction, can be determined. However, this differentiation is of academic interest only, for in either case an attempt to

remove the obstruction by surgical means is the only procedure that offers any chance for permanent relief. Vincent thinks that although a ventriculogram, plus the use of colored dyes to determine whether or not free communication exists between the lateral ventricles, can show whether or not the third ventricle is dilated, by this means the neurosurgeon cannot be sure whether the obstruction lies in the anterior or the posterior part of the aqueduct. He advises an encephalogram to discover whether or not the fourth ventricle can be filled from below. I believe that an encephalogram should never be used under such circumstances. Encephalography is a dangerous procedure if intracranial tension is high, and tumors of the third ventricle are always accompanied by increased pressure. Furthermore, as Vincent admits, when tumors in the aqueduct are present it is often difficult to fill the fourth ventricle by lumbar insufflation. Under such circumstances it is suggested that intracranial tension first be lowered by direct ventricular drainage. This makes lumbar puncture comparatively safe, and relief of pressure may allow filling of the fourth ventricle if an encephalography is promptly performed. The point that Vincent makes is an important one; namely, to attack by the suboccipital route a tumor blocking the aqueduct from above is a useless and usually a fatal procedure. It was gathered from his comments: (1) that he considered that tumors blocking the upper part of the aqueduct cannot be localized in many instances by ventriculography, and (2) that they are usually inoperable and had better be left alone to avoid an operative mortality. However, I believe that a properly taken and filmed ventriculogram of a tumor of the third ventricle will rarely fail to give all the information necessary for accurate outline of the operative approach. I do agree that tumors in and around the aqueduct present almost insuperable problems to surgical removal, but they have been successfully extirpated by various surgeons. If nothing is done, the patient with such a lesion is doomed; if the patient wishes it, he should be given the chance. I am also in accord with Vincent's opinion that, faced with a patient showing only increased pressure and no neurologic localizing signs, if a ventriculogram shows a dilated third ventricle the operative attack should be carried out through the suboccipital approach if the surgeon feels that such a procedure is indicated.

Ayala, in discussing the symptoms of cerebellar tumors, stated that such tumors as a rule produce symptoms that easily distinguish them from lesions above the tentorium. Although the x-rays and other methods may give evidence of important localizing value, the diagnosis can usually be made from the neurologic signs alone. The underlying pathologic basis for the symptoms produced by tumors situated in this region is the same whether the growth is located within or without the

cerebellum or in the bulb, for tumors in this area more than in any other intracranial region involve the anatomic integrity and physiologic functions of important vegetative and coordination centers. The space in which these tumors are found is relatively narrow, and for this reason interference with the circulation of the cerebrospinal fluid soon occurs. This accounts for the relatively early appearance of symptoms of increased intracranial pressure.

There are three groups of symptoms produced by lesions of the posterior fossa: (1) those of an irritative or paralytic nature, caused by the presence of the tumor itself; (2) symptoms resulting from obstructive hydrocephalus, which accompanies the tumor, and (3) neighborhood symptoms due to pressure by the tumor on adjacent structures. The site of origin of the tumor and the rapidity and direction of its growth may modify the order of the appearance of these three groups of symptoms. As a rule, however, there is no relationship between the character and variety of the clinical signs and the size of the tumor. This is due to the fact that the brain can apparently adjust itself to the presence of a tumor, and that undamaged areas can to a certain degree take over the functions of the parts involved. In this way, slow-growing tumors may reach a large size without producing a cleancut picture of cerebellar involvement.

Although Ayala believes that one should not speak of a syndrome as definitely pathognomonic of a tumor situated in any particular cerebellar area, nevertheless, there are groupings of clinical symptoms that appear with sufficient frequency to permit of approximate localization.

The first of these clinical forms is characterized by the rather sudden appearance and then slow development for a long period of symptoms suggesting bulbar involvement.

In the second group are the angle tumors in which the first symptoms are referred to the eighth and seventh nerves, with cerebellar involvement coming on later.

The third type is made up of intracerebellar tumors producing unmistakable cerebellar and vestibular signs from the beginning, with symptoms referable to the pyramidal, sensory and vegetative pathways appearing later.

The fourth group consists of the midline cerebellar tumors or tumors of the fourth ventricle, giving bilateral vestibular and cerebellar symptoms together with evidence of involvement of the nuclei of the cranial nerves in these regions. Owing to the position of these tumors, the clinical picture may develop abruptly, as they interfere with the circulation of the cerebrospinal fluid.

Kennedy outlined the major clinical features of tumors of the frontal and temporosphenoidal lobes. The localizing signs of deterioration in the function of these areas are often vague and misleading. Changes in personality are usually more frequent than from lesions elsewhere. An inapt jocosity may appear early, passing through failure in general memory to hebetude, with frequent yawning and partial stupor. This drowsiness resembles true sleep less than does that resulting from hypothalamic neoplasms. Frequent loss of sphincter control is characteristic and cannot always be ascribed to mental and emotional change. Occasionally tonic perseveration of muscular action is seen contralaterally, especially when the anterior part of the corpus callosum is involved. The most characteristic station is titubation on the heels with retropulsion. Compression backward often produces mild contralateral pyramidal signs, but a meningioma placed anteriorly may press across the midline of the brain, giving rise to similar motor reduction and reflex changes on the same side as the main growth. A difficulty in the emission of speech without internal language involvement may occur where cerebral dominance has been appropriately determined by the patient's stock and handedness. However, these signs may be equivocal. The following syndrome, when present, is pathognomonic of a tumor of the frontal lobe: ipsolateral retrobulbar neuritis with central scotoma and great reduction in visual acuity, associated with contralateral papilledema and ipsolateral anosmia.

Temporosphenoidal tumors may produce a rather more complex group of symptoms, for in this region are centers for speech, taste and smell, while deeply seated tumors impinge on the optic radiations, producing homonymous hemianopic visual field defects. When hemiplegia develops, the face is more markedly affected than either the arm or the leg. Characteristically, speech defects consist in loss of recollection of names and of errors in naming. Motor speech is not involved and word deafness infrequently occurs.

Following after this outline of the symptomatology of tumors of the brain came a discussion of their pathology by Bailey, Penfield and Roussy and Oberling.

Bailey considered particularly the gliomatous tumors, dividing them into three great groups, the medulloblastomas, glioblastomas and astrocytomas. These three types differ widely in age at onset, site of origin and biologic behavior.

The medulloblastoma is almost exclusively a tumor of the midcerebellum in children. Its clinical evolution is rapid, the average length of life of the patient from onset of symptoms to death being about fifteen months. Microscopically, the tumor is composed mainly of small cells with oval hyperchromatic nuclei and very little cytoplasm.

Pseudorosettes occur, and spongioblastic and neuroblastic cell types are frequently encountered. The origin of these tumors seems to be confirmed, and from both a pathologic and a clinical basis they seem to form a well defined group composing about 10 per cent of all gliomas. On rare occasions a tumor of this type may appear in the cerebral hemisphere in adults.

The glioblastoma multiforme, the spongioblastoma of Globus and Strauss, occurs almost exclusively in the cerebral hemisphere in adults. The growth of these tumors is rapid, the average length of the clinical course between onset of symptoms and death of the patient being about twelve months. The symptoms often appear abruptly, because hemorrhage and thrombotic softening in the tumor are common. The tumor is composed microscopically of anaplastic neuroglia cells, and has all the characteristics of rapid growth: numerous mitotic figures, giant cells and marked vascularity. This group makes up from 20 to 30 per cent of all gliomas.

The third great family is that of the astrocytomas. This is a slow-growing, indolent tumor having a marked tendency to undergo liquefaction and cyst formation. The entire tumor may become cystic except for a nodule remaining in the wall. If the cyst is evacuated and this nubbin is completely removed, the tumor will not recur. These tumors compose about 30 per cent of all gliomas.

The importance of knowing the probable histologic nature of the tumor before operation is self-evident, for on this knowledge depends in great part the way in which the tumor will be attacked. At present, by the use of supravital stains it is possible to determine at once with marked accuracy the type of tumor encountered. Based on this knowledge the operator can decide how far he must go in attempting to extirpate the tumor. If, for example, an astrocytoma is present, a much more determined effect should be made completely to remove the growth, for total excision is not followed by recurrence, whereas an infiltrating spongioblastoma would require an extensive block dissection for its extirpation, and even then a recurrence of the neoplasm is extremely likely to occur.

Following on this outline of the various types of tumors arising from the neuroglial structure of the brain, Penfield discussed the histopathology of those originating from the membranes surrounding the nerve structures—the dura and the nerve sheaths. It is his opinion that, from the standpoint of neurology and neurosurgery, it is important to adopt a generally recognized nomenclature for these tumors. Changes from the generally accepted terminology describing any neoplasm are to be deprecated, especially when the newly adopted terms do not

express an important recent discovery bearing on the embryology or histology of the tumor in question.

The first group of these tumors of the neural envelopes considered by Penfield is that most frequently encountered, the meningeal fibroblastoma. These have hitherto been called psammomas, dural endotheliomas or meningiomas. Tumors of this type form a well recognized group. In 1903, Schmidt recognized that they originated from arachnoid fibroblasts invading the dura. The term dural sarcoma should be avoided in designating such tumors as it suggests a malignant tendency, whereas they are entirely benign. Dural endothelioma, meningioma and psammoma are acceptable terms as they indicate correctly their origin and development.

Bailey and Bucy (1931) have recently introduced nine subdivisions into the classification of meningeal tumors. These authors include angioblastomas, melanoblastomas, lipomas and diffuse sarcomas of the pia mater in their subgroups, four important tumor types that might well be classified as meningiomas. Penfield believes strongly that these four groups do not belong in the same classification with the dural endotheliomas. The other five subdivisions that they suggested, the mesenchymatous, meningotheliomatous, fibroblastic, psammomatous and osteoblastic types, however, all may well be placed in the group Penfield designates as a fibroblastic meningioma. That fibroblastic meningiomas may be divided into such subdivisions is good evidence of the developmental possibilities of the meninges, a fact that Bailey and Bucy admit. However, Penfield believes that these different groups are all variations of the same tumor of which the typical cell, when sufficiently differentiated, has all the characteristics of a fibroblast. It is for this reason that Mallory, in 1920, called these tumors arachnoid fibroblastomas, and Penfield in complete agreement with him designated them as fibroblastomas, substituting the term meningeal for arachnoid in certain instances in which the growth had no great connection with the arachnoid.

Sarcomas of the dura should be mentioned, as these tumors show a structure sometimes reminiscent of the meninges and meningeal fibroblastomas. Sarcoma of the leptomeninges, also a rare neoplasm, metastasizes through the cerebrospinal fluid, as is to be expected.

Tumors of the nerve sheaths fall into three groups. The problem is one of terminology and identity. The first type is the perineurial fibroblastoma. The outstanding histologic characteristic of these tumors is the presence in them of long hairlike fibrils. They are reticulin fibrils. These hairlike fibrils pass off continuously into the leptomeninges, showing the identity of their structure with the collagen structures of the leptomeninges.

The second group consists of the peripheral gliomas, which are exceedingly rare. They rise from the sheath of Schwann cells or their precursors, but do not in any way resemble perineurial fibroblastomas.

Further consideration of the pathology of tumors of the brain was carried on by Roussy and Oberling. Based on the examination of about 250 such lesions, these authors divided them into five groups: gliomas, ependymochoroidal tumors, ganglioneuromas, neurospongiomas and neuro-epitheliomas. Gliomas are again subdivided into three types: astrocytomas, oligodendrogliomas and glioblastomas. Although Roussy and Oberling agree that the distinction between fibrillary and protoplasmic astrocytes should be abandoned, they then proceed to develop five different groups depending on various histologic variations, the size and shape of cells, the amount of fibrous tissue and other factors. The oligodendrogliomas, they admit, have been so well described by Bailey and others that they only need subdivision into three groups. The group of tumors formerly known as the spongioblastoma multiforme they call glioblastoma.

In the group of ependymochoroidal tumors they believe that distinction should be made between the ependymal and the choroidal types. Three subgroups of ependymal and two of the choroidal tumors can be differentiated. The tumors that they term neurospongiomas correspond to the medulloblastomas of Bailey and Cushing.

Lastly, under the name of neuro-epitheliomas are described tumors in which are found a mixture of cell types usually considered to be of neuro-epithelial derivation and produced by the differentiation of spongioblastic and neuroblastic elements. These authors believe that a strict definition should be established for these tumors, for it is in this group that the greatest confusion has occurred. Hitherto, the term neuroepithelioma has been given to a great variety of tumors, as gliomas with ependymal inclusions, pseudopapillary astrocytomas, ependymochoroidal tumors and neurospongiomas.

I think that the classification suggested by Roussy and Oberling tends to confuse rather than to simplify the situation with regard to tumors of the brain.

Following these papers dealing with the pathologic variations of tumors of the brain, consideration was given to mechanical aids in the diagnosis of these lesions. Pfeifer described the technic of puncture of the brain for diagnosis and localization of tumors. Frankly, I had hoped that this procedure had been abandoned. So many more satisfactory methods of localization are available that puncture of the brain might well be discarded. Pfeifer trephines the skull in the suspected area, plunges a needle having a lumen of 1 mm. into the brain and removes a small core of tissues sucked into the needle by aspiration. This specimen is then prepared and studied microscopically. If there

are no localizing signs, the silent areas of the brain must be thoroughly needled. The cerebellum may also be punctured, but never more than twice at one sitting. Pfeifer states that the principal dangers are hemorrhages into vascular lesions; he has had eleven deaths from this cause in a series of several thousand punctures. Curiously enough, he states that the middle meningeal artery is most often damaged. I would have thought that this vessel, at least, could have been avoided. I subscribe heartily to Pfeifer's warning as to the possibility of hemorrhage in the tumor following puncture, with serious consequences to the patient. I would also add that even after the successful removal of the sliver of brain tissue a positive pathologic diagnosis may frequently be difficult.

Schüller gave a brief review of the changes produced in the cranial bones by an intracranial tumor that can be identified by roentgen examination. There was nothing particularly new described, but when one considered the vast amount of experience with which Schüller could support his statements and that certain of the diagnostic findings in common use had been original with him, the summary he gave was impressively complete.

Tumors of the brain produce two main types of changes in the cranial bones: those due to increased pressure and local variations caused by the position of the tumor.

Increased intracranial pressure causes erosion of the inner table, with generalized or local convolutional atrophy. Separation of the sutures is seen. The base of the skull presents many small depressions, round, with sharply defined borders, which are caused by small cerebral hernias resulting from the intracranial pressure. The foramina at the base of the skull are enlarged; the shadows of the pacchionian bodies and the sinuses together with the venous and emissary channels in the diploe may stand out more clearly. The sella turcica is enlarged. Curiously enough, however, Schüller did not place much stress on the erosion of the posterior clinoid processes, which occurs as internal hydrocephalus develops and the third ventricle distends downward.

The local signs of the presence of a tumor are calcification within the growth, a circumscribed erosion and thickening or infiltration of the skull, with an increase in the size of the shadows from venous channels and pacchionian bodies, or a pneumatocele from encroachment on the paranasal sinuses.

In addition, Schüller outlined roentgen changes in the skull in neurofibromatosis of von Recklinghausen's disease and in generalized xanthomatosis. The lantern slides that he showed in his demonstration were extremely illustrative.

Sachs brought up the question of the reliability of roentgen evidence in the localization of tumors and to what degree evidence from this

source could be trusted if it ran counter to the neurologic signs. Certain cases of cerebellar tumor, particularly when the condition is far advanced, cause internal hydrocephalus. As a result of this ventricular distention, the third ventricle is enlarged downward. Consequently, the posterior clinoid processes and eventually the whole sella may be eroded, and the roentgen picture may be typically that of a suprasellar lesion. Furthermore, clinical evidence of pituitary dysfunction may be present from pressure on the gland. If the obstructing lesion in the posterior fossa is small and in the midline, cerebellar symptoms may be indefinite. Under such conditions it should always be kept in mind that a midline cerebellar tumor can produce sellar erosion. A ventriculogram should be made to determine whether the lesion lies above or below the tentorium.

Occasionally a case may be encountered in which pressure markings, convolutional atrophy, develop with great rapidity. Accumulation of fluid in the subarachnoid space may account for such a change, and consequently the roentgen diagnosis of a pressure skull must be balanced against the clinical findings on neurologic examination.

Lastly, it must always be remembered in planning the surgical approach to a tumor of the brain localized by calcification within the growth that only part of the tumor may be calcified and that actually the mass may be much larger than the roentgen findings suggest. This is an important fact and worthy of careful consideration. The neurosurgeon should always turn down a large flap under such conditions, much larger than the roentgen findings would seem to require. Unless this is done he will inevitably find himself cramped for room in his operative maneuvers to extirpate the mass, and may find himself in the awkward situation of being compelled to enlarge his osteoplastic flap before the tumor can be dealt with satisfactorily.

Stenvers called attention to the changes in the temporal bone, erosion of the petrous ridge and about the internal auditory meatus, that may be produced by lesions in this region, particularly angle tumors. However, it is my experience that, although such erosions may occur, they are not always due to tumors and may be noted on the opposite side of the skull to that on which the tumor is situated. This finding should never be given much consideration unless it fits in with the clinical picture. As Stenvers stated, there is no connection between the amount of erosion and the size of the tumor.

More important, in my opinion, are the general signs of tumors of the posterior fossa which may be demonstrable on an x-ray picture. Stenvers emphasizes the convolutional atrophy seen on the inner table of the vault of the skull and the secondary changes about the sella turcica. In both of these conditions it is the mechanical factor of increased intracranial pressure that causes the changes in the bone. As

stated in discussing the papers of Schüller and Sachs, it is important for the neurologic surgeon to realize that if internal hydrocephalus accompanies a tumor of the posterior fossa, and such is commonly the case, the resulting dilatation of the third ventricle can produce an erosion of the posterior clinoids indistinguishable from that caused by a suprasellar tumor. As Stenvers says, the presence of a primary intrasellar tumor may often be determined by the downward extension of the sella and its encroachment on the sphenoid sinus. But a lesion in the suprasellar position usually affects only the posterior clinoids. It is in the differential diagnosis between tumors in this situation and in the posterior fossa that the roentgen findings may be misleading.

The next three papers were concerned with the use of the insufflation of air into the subarachnoid spaces and ventricles for the localization of intracranial tumors.

Guttmann outlined the value of encephalography, lumbar insufflation of air, particularly when the tumor lay above the tentorium. By this means it is possible to determine the presence of a tumor before signs of intracranial pressure develop. Indeed it is particularly in borderline diagnoses, between tumor and vascular disease for example, that encephalography is especially valuable. Guttmann described the common encephalographic findings connoting the presence of a hemispheric lesion, a filling defect in or complete obliteration of the lateral ventricle on the same side as the tumor. The third ventricle is usually shifted from its midline position, and with the lateral ventricle of the uninvolved hemisphere is displaced outward away from the site of the growth. Guttmann states that occasionally if a cystic degenerated tumor is present the ventricles may be shifted toward the side of the tumor and the corresponding lateral ventricle may be dilated instead of obstructed. I have never seen this ipsolateral ventricular dilatation occur, except in a case in which the tumor lay wholly within the ventricle and partially obstructed one foramen of Monro. In this instance the outline of the tumor was easily discernible within the shadow of the air in the lateral ventricle.

Tumors of the posterior fossa usually produce more or less symmetrical dilatation of the lateral and third ventricles above the point of obstruction. If the tumor lies in the cerebellar hemisphere or in the cerebellopontile angle, the overlying posterior horn of the lateral ventricle may be elevated a little above the contralateral posterior horn. This again, in my experience, is not a constant finding. Furthermore, it must be remembered, as Guttmann emphasizes, that certain lesions of the posterior fossa, acoustic tumors for example, may grow so slowly that no or only slight interference with the cerebrospinal circulation occurs, and internal hydrocephalus is not produced.

Foerster, in discussing the localization of midline tumors and tumors of the posterior fossa by ventriculography, made a definite statement that I think is of importance; namely, the use of lumbar or suboccipital insufflation of air in the presence of choked disks or other evidence of intracranial pressure is dangerous and should be avoided. Ventriculography is the method of choice under such circumstances. With this opinion I am in hearty agreement. In the localization of tumors of the midbrain, the defects in the shadow of air in the third ventricle are the determining factors. At times the exact definition of this shadow is difficult to make out. Under such circumstances it may be important to discover whether interventricular communication between the lateral ventricles through the foramina of Monro can occur. The injection of iodized oil (I have used methyl blue dye with success) into one ventricle and its recovery from the opposite lateral ventricle will determine this point. If the foramina of Monro can be proved to be patulous, the tumor must lie in the midline below this level and the upper part of the third ventricle should fill with air.

Foerster spoke of pseudotumor cerebri in which from general edema of the brain the ventricles may be small in size but regular in outline and in their normal position in the midbrain. He also repeated Guttmann's statement that in cystic degenerated hemispheric tumors the lateral ventricle on the side of the lesion may be dilated.

In pseudotumors of the posterior fossa, described in this country by Horrax as "arachnitis" of the cisterna magna, the entire ventricular system, the lateral, third and fourth ventricles and the aqueduct are shown to be dilated on ventriculography. Differential diagnosis of the cause of the block, whether from tumor or arachnitis, is, of course, possible only by operative exposure.

In the determination of the types of hydrocephalus, whether obstructive or nonobstructive, a ventriculogram alone is inadequate. Resorption tests with sodium iodide are essential to demonstrate with accuracy the point of obstruction.

The papers of Guttmann and Foerster were illustrated with remarkably good lantern slides.

Grant considered the indications for and the comparative value of encephalography and ventriculography. The chief indication for ventriculography is increased intracranial pressure, the cause for which cannot be accurately localized. In performing ventriculography the most important point in technic is the removal of as much fluid as possible. Unless all fluid is withdrawn, a part of it may be trapped in the horn of a ventricle, which on the x-ray picture may simulate a filling defect and the presence of a tumor. All fluid can most effectively be aspirated if both ventricles are tapped. Furthermore, by a

bilateral tap the amount of fluid in each ventricle can be determined, and by comparison of their capacity a shrewd guess can be made as to their relative size. A cerebral hemispheric tumor almost always is situated on the side of the smaller ventricle. Bilateral hydrocephalus means a midline tumor either above or below the tentorium. Thus by bilateral ventricular tap and estimation of the relative size of the lateral ventricles, ventricular estimation, it is often possible to localize the tumor without the necessity for injecting air.

One hundred and sixty instances of ventriculography and fifty-two of ventricular estimation form the basis of this part of the report. Of the 160 ventriculograms, the tumor was localized and removed in ninety-three. In forty-five cases the procedure verified the clinical findings, but in the forty-eight remaining instances ventriculography afforded the only possible means of localization. Errors in technic caused a failure of the method in seventeen cases, or 10.6 per cent. The mortality following this procedure was 6.2 per cent. In fifty-two cases of ventricular estimation, symmetrical ventricular distention was proved without injection of air in thirteen and asymmetry in thirty-nine. In thirty-five of the thirty-nine cases with lateral ventricles of unequal size the tumor was subsequently found to be in the hemisphere having the smaller ventricle.

Three hundred and twenty-five cases in which encephalography was performed formed the basis for the second part of the report. The technic of encephalography is simpler than that of ventriculography, but lumbar insufflation is followed by a much more severe reaction on the part of the patient. Furthermore, encephalography is not safe if increased intracranial pressure is present, as, for example, in tumors of the brain. When results of encephalography and ventriculography are compared in the group with pressure or tumor of the brain, it is found that imperfect filling of the lateral ventricles and therefore failure to localize the tumor occurred in 19.5 per cent of cases following encephalography as compared with 10.6 per cent after ventriculography.

A group of seventy-two cases of idiopathic epilepsy, one of fifty-one cases of traumatic epilepsy and one of forty-one cases of posttraumatic headache were analyzed. The films in each group were compared to determine whether or not each of these conditions produced typical changes in the brain, which would permit a differential diagnosis by encephalography. Of the seventy-two cases of idiopathic epilepsy subjected to encephalography, in sixteen the plates were considered normal; atrophy was the principal finding in forty, arachnitis in sixteen and lateral ventricular asymmetry in four. Of fifty-one cases of posttraumatic epilepsy, the encephalograms were considered normal in five, atrophy was the principle finding in twenty-eight, arachnitis

occurred in eighteen, and lateral ventricular asymmetry occurred in twenty-three. Of forty-one cases of posttraumatic headache, the encephalogram was normal in six, atrophy was the principal finding in thirty-two, arachnitis was present in three, and lateral ventricular asymmetry was present in six.

Study of the encephalographic films in the epileptic group, in an attempt to correlate the findings with the severity and frequency of the convulsions, showed that there seemed to be no definite connection between the changes shown in the brain and the violence, character or number of the fits. From the therapeutic standpoint, the benefits of encephalography are most marked in the group with posttraumatic headache. However, surprisingly good results occurred following encephalography in epileptic patients. Therefore, the fact that encephalography has been performed must always be kept in mind when other forms of treatment, as dehydration, diet, etc., are instituted following a diagnostic encephalogram.

Moniz described his technic of arterial encephalography for the localization of tumors of the brain. Briefly, this technic consists in the isolation of one common carotid artery and the injection into it of from 6 to 9 cc. of a 25 per cent solution of chemically pure sodium iodide. This technic is carried out on the radiographic table with the head in proper position, and as the last of the solution is injected the films are made. By this method the intracranial blood vessels are outlined on the film. The normal contour and position of the cerebral vascular tree are known, and deviations from the normal give evidence of the location of the tumor. This procedure is similar to encephalography or ventriculography except for the fact that shifts in position of the cerebral vascular tree instead of the fluid spaces of the brain are used as indications of the position of the neoplasm.

Moniz uses phenobarbital as a preoperative sedative because of the frequency with which tonic or clonic convulsive seizures accompany the injection of the sodium iodide. He believes that advanced arteriosclerosis, uremia or other toxic conditions are contraindications to this procedure.

I have never employed this diagnostic method. The use of air has proved sufficiently satisfactory and is so simple to carry out that the use of arterial encephalography did not seem necessary. I hesitated to use a method that involved even momentary closure of one common carotid and the injection of a foreign material into the cerebral vasculature. Moniz' early reports mentioned epileptiform seizures as a not uncommon immediate complication of the injection. But since seeing his results, especially as illustrated by the well-nigh perfect lantern slides he exhibited, I am almost persuaded to attempt this technic

in a suitable case. It would seem likely that by this method a localization could be made without producing the after-effects of increased cranial pressure, which are unquestionably a hazard when the injection of air is used.

Kafka and Fremont-Smith described the value of careful examination of the cerebrospinal fluid to determine the presence and localization of a tumor of the brain, which may produce either cellular or chemical changes in the fluid. The presence of tumor cells is probably one of the most important and also one of the rarest of the cellular variations noted. An increase in the protein content of the spinal fluid is the chemical change seen most frequently in conjunction with a tumor of the brain. These speakers also emphasized the importance of comparing the amount of protein in fluid obtained from such different areas as the lumbar sac, cisterna magna and ventricles. Fremont-Smith said that supratentorial pressure should be relieved by ventricular tap before a lumbar puncture is attempted, because of the danger attending lumbar puncture in the presence of increased intracranial tension. This procedure achieves a threefold result: dangerous supratentorial pressure is relieved and lumbar puncture is made safe, fluid is obtained from two areas for the comparison of protein content, and, if manometers are attached to the needles and the jugular veins are compressed, evidence of a block may be found in the ventricular system suggesting the presence and location of a tumor. I agree that the estimation of protein in the cerebrospinal fluid helps in the diagnosis of tumor of the brain. However, if a ventricular tap is to be done anyway to obtain fluid for comparison with fluid from other loci, I believe that ventriculography might just as well be performed, so that the position of the tumor may be verified accurately.

Bohnenkamp and Schmäh presented an interesting device by which the resistance of various segments of the brain to an electric current may be measured. Normal tissue of the brain shows a definite change in potential when subjected to such a current, but the presence of a tumor in any region of the brain definitely changes the resistance to electricity. The apparatus described consists of a closely fitting metal helmet made of thin strips that run laterally from one side of the head to the other. A needle introduced into the suboccipital region forms the second point of contact. In a series of thirty-nine cases, four autopsies and one patient on whom an operation was performed, the changes in the electrical resistance suggested a lesion in the same area indicated by the clinical signs or other findings. Personally, I am sure that there is a definite value in the determination of the electrical resistance of the brain. I have worked on the same problem from a different angle and can confirm the findings of Bohnenkamp and Schmäh.

Cushing's summary of the results of his operative attack on tumors of the brain was unquestionably the most important and most striking paper of the first day's meeting. His statistics were probably "caviar" to most of the neurologists and psychiatrists, but to the neurosurgeons they were a revelation and a source of enviable satisfaction. Even today it is often difficult to convince some neurologists of the frequency of intracranial tumor and of the possibilities for relief which modern neurosurgery offers. Consequently, they hesitate to make a diagnosis of tumor of the brain until the presence of a neoplasm is shown so clearly that any alert fourth year medical student, trained in a school where neurosurgery is done, could detect it. The patient's chance of satisfactory operative result is considerably lessened by this waste of time.

Cushing's figures show that in the past thirty years he has performed 3,292 operations on 2,366 patients. Tumor of the brain was verified by microscopic examination of tissue in 1,870 of these patients. The operative mortality for this entire group was 11.9 per cent. In the past three years, 635 operations were done on 478 patients. The group of verified tumors of the brain numbered 412 cases; that of unverified tumors, 66. The operative mortality for both groups was 8.7 per cent. Aside from the fact that these figures represent the largest group of tumors of the brain falling within the experience of one surgeon, the low rate of mortality is most remarkable. Coming from a clinic wherein a tumor of the brain is suspected in practically every case in which an operation is performed, and where the term "cranial operation" does not include decompressions for trauma, epilepsy or trigeminal neuralgia (inclusion of these relatively simple operative procedures will lower the mortality percentage materially), these figures give neurosurgeons a standard that they must be skilful indeed to equal or better. Such statistics as these justify the handling of surgical intervention in the brain by properly trained men. Any surgeon can turn back a bone flap or expose a tumor by craniectomy after a neurologist has made the localization, but the neurosurgeon knows and the general surgeon is gradually becoming convinced that this is only the beginning of the struggle. It is important to be able to handle properly the intracranial pressure before, during and after the operation, to be able to recognize the type of tumor, to decide whether a determined effort should be made to extirpate it and to know how to do this with the least possible damage to the surrounding brain. Judgment in such matters is developed only by the experience that comes from undeviating devotion to this field of surgery.

De Martel stressed the importance of the proper handling of postoperative intracranial pressure. This condition is ushered in by hyper-

thermia and arterial hypotension. He believes that the increased tension exerts pressure on the centers of the midbrain that control temperature and vasomotor tone, and that drainage of the cerebrospinal fluid after operation keeps the intracranial pressure within normal limits and prevents hyperthermal and hypotensive crises. I am able to confirm de Martel's opinion by my own repeated observations of the marked benefit that follows ventricular or lumbar tap in the first twenty-four hours after operation. De Martel also believes that drainage of the subarachnoid space should be begun at the time the wound is closed and should be continued for from twenty-four to forty-eight hours. I do not think that this increases the chances of infection, and certainly release of the fluid does much to prevent the onset of the pressure that inevitably results from the traumatic edema of the brain incident to operative manipulation for the extirpation of the tumor.

Olivecrona pointed out that, clinically at least, only two types of gliomatous tumors are found in the cerebral hemispheres: the malignant and the relatively benign. In the malignant gliomas, development is rapid, psychic symptoms are prominent, and intracranial hypertension appears early. Neurologic examination indicates a rapidly expanding lesion. Olivecrona believes that, in this group of tumors, surgical intervention promises little or no hope of permanent cure and is justified only to verify the type of tumor present. On the other hand, the benign gliomas have a much more favorable prognosis. Clinically, they develop slowly, and the results of operative removal are generally satisfactory. Olivecrona's statistics show an operative mortality of 20 per cent, with a case mortality about 15 per cent higher because of recurrence of the tumor. All of the other patients have survived for a year and a half, and at least one third of them have recovered so completely as to be able to resume their occupations.

Puusepp described his method of surgical attack on infiltrating gliomas. An osteoplastic flap is turned back to expose the tumor, the dura is opened, and the exact position and depth of the growth are determined by needling the brain. A wide transcortical incision is then made, and part of the tumor is removed for verification. The dura is left open, the bone flap is removed, and the skin is sutured. After three or four weeks, a second operation is performed, at which time it is found that the glioma has come to the surface through the cortical incision and may be removed with ease, as it is now readily distinguishable from normal tissue of the brain. In four cases in which this procedure was followed, Puusepp states that there was no recurrence after from three to five years. In one case it was necessary to remove a glioma from the right temporal lobe three times, with inter-

vals of a year and a half between each operation. During these periods the patient was well and continued to teach school.

I am rather skeptical of Puusepp's claim that the tumor will thrust its way to the surface if the cortex is incised, the dura left open, and the bone flap removed. Furthermore, it has been my experience, with rapidly infiltrating gliomas, and especially spongioblastomas, that it is just as difficult to distinguish between tumor and normal tissue of the brain at a second operation as it was originally. I regret that Puusepp failed to give the exact pathologic diagnosis of the tumors successfully treated by this method. It is conceivable that they were slow-growing tumors of the astrocytic or oligodendroglial group, and hence repeated partial removal and decompression relieved the symptoms sufficiently for him to report a cure. Possibly complete extirpation with permanent cure might have been achieved at the first operation. My own experience makes me doubt the value of this method of palliation even in spongioblastomas, to which it would seem most applicable.

The next three papers read discussed the value of the roentgen rays and radium for the treatment of tumors of the brain. Béclère divides intracranial tumors into three groups: those originating in the pituitary fossa or its immediate vicinity, verified tumors of the cerebral or cerebellar hemispheres and unverified tumors. The first group includes pituitary adenomas, tumors of Rathke's pouch and suprasellar meningiomas, of which the pituitary adenomas alone are amenable to this type of treatment. Béclère is certain that cures by roentgen therapy may be effected in pituitary adenomas, and I agree entirely with this opinion, although if there is loss of vision I believe that operative verification is advisable before treatment is started. A transfrontal craniotomy is a relatively simple procedure, and a cyst, if found, may be tapped and immediate improvement obtained by the rapid relief of pressure on the optic nerves. My experience has been that the roentgen rays have less beneficial effect on pituitary cysts than on semisolid adenomas. It is often impossible to determine by clinical signs and roentgen films alone the type of intrasellar tumor present. Tumors of Rathke's pouch, cystic adenomas and suprasellar meningiomas are not affected by the roentgen rays. If all pituitary tumors are treated without operative verification, much vision may be sacrified before lack of improvement to roentgen treatment indicates that an insensitive type of pituitary growth is present. In my opinion, roentgen therapy is justified as a primary measure only when there is no loss of vision. In any event, operative procedure verifies the type of lesion, allows at least partial removal and so prevents further loss of vision by pressure from the tumor. Certainly, roentgen treatment should always follow operative intervention to prevent recurrence.

The second group includes tumors of the central nervous system, the cranial nerves and the meninges. Béclère says that cure by roentgen therapy alone has never been proved for any of these tumors, but is certain that postoperative therapy has often been valuable in relieving symptoms, preventing recurrences and prolonging life. I am not quite as enthusiastic about postoperative roentgen therapy for this type of tumor of the brain. I am sure that meningiomas, acoustic neuromas, astrocytomas and oligodendrogliomas are not affected favorably. Medulloblastomas are undoubtedly controlled by this means, and a few spongioblastomas may be. There is always one factor that must be considered in the evaluation of roentgen therapy. If treatment is instituted shortly after operation, it may receive credit for the improvement in symptoms actually due to the decompression, which is almost universally performed after the exposure and partial or complete removal of a glioma. I quite agree with the opinion of a wise and experienced roentgenologist of my acquaintance, who admitted that a fair test of the efficiency of postoperative roentgen treatment can be made only after all improvement following operation and decompression has ceased and definite symptoms of a recurrence of the tumor are appearing. If roentgen treatment checks the progress of the symptoms or produces improvement, then, and only then, can it be said that this therapy is effective.

The claims for the therapeutic efficiency of roentgen treatment in the third group of cases in which, because of intracranial tension, there is assumed to be a tumor are also open to question in the absence of definite pathologic confirmation. As Béclère acknowledged, many of these patients may have had an arachnoid cyst, a serous meningitis or a hydrocephalus from an obscure cause. In his hands roentgen therapy has apparently been successful. My experience has been that some of these disorders clear up spontaneously without treatment. I have never seen roentgen therapy have the slightest effect on hydrocephalic infants, although such patients should be ideal subjects for this treatment if, as Béclère suggests, the rays cut down the secretion of the cerebrospinal fluid by the choroid plexus.

Cairns and Cade described the results of their treatment of verified tumors of the brain with radium. After animal experimentation to determine the effect of radium on the normal brain, the treatment was originally carried out by direct implantation of radium needles into the tumor. This method was later abandoned because it seemed impossible to obtain uniform radiation and because, in one vascular glioma, the presence of radium apparently precipitated a fatal hemorrhage. At the present time the radium is applied externally and held in place by a rubber dressing. A series of ten verified spongioblastomas treated up to the end of 1930 was presented. In six patients

radium therapy was not successful and did not prolong life. One patient is alive fifteen months after treatment but shows evidence of extension of the tumor into the opposite cerebral hemisphere. Two patients have apparently complete cessation of symptoms eighteen months after treatment, and a fourth has recovered entirely from a right hemiplegia and aphasia two years after the completion of the radium therapy.

This was a conservative, carefully considered and important contribution. The results seem worthy of thoughtful examination. Furthermore, Cairns and Cade had opportunity to make postmortem studies of tumors thus treated. On microscopic examination they found large areas of necrosis and noted that there was active cellular proliferation only in the parts of the tumors inaccessible to the application of radium. In the last analysis, postmortem study alone can determine the real efficiency of roentgen or radium therapy. Clinical evidence of improvement may be due to the operative decompression and the partial removal of the growth. If the tumor is verified and studied before any type of therapy is instituted and if tumor tissue obtained at necropsy is reexamined and shows evidence of death of tumor cells, the real effect of this treatment can be definitely estimated. It is vital, therefore, that the neurosurgeon verify the lesion at the first operation, so that the type and structure of the untreated tumor can be recognized and the changes due to roentgen or radium therapy can be accurately determined. When this has been done in a sufficiently large and varied group of cases, the true value of this treatment will be known.

Hirsch, using as a basis a series of 132 cases in which operation was performed, outlined his results in the treatment of pituitary tumors with radiation. His was the point of view of the surgeon who saw the lesion, verified it and then noted the results of radium therapy, and in my opinion his statements were pertinent and of great importance. He believes that radium therapy should be used only in conjunction with surgical intervention. Radiation will prevent recurrence and reduce the size of solid tumors that cannot be removed at operation. It will hinder the refilling of a cystic tumor after the cyst has been drained surgically. However, Hirsch does not believe that radium therapy will of itself affect a cyst. In a few cases he has used radium therapy without operation on tumors he believed to be solid, which were not accompanied by visual loss. If a pituitary tumor is affecting vision he relieves pressure on the optic nerves by prompt surgical intervention, and only later attempts to prevent recurrence by radium therapy.

Putnam outlined succinctly the knowledge of the physiologic action of the internal secretions of the two intracranial glands, the pineal

and the pituitary. The functions of the pineal gland, assuming that this organ is a gland, are entirely unknown. Neither the extirpation nor the administration of this gland will produce the syndrome of precocious adolescence in animals. It is impossible to say from either pathologic or experimental evidence whether this syndrome is due to hyperfunction or to hypofunction of the pineal gland or of contiguous structures. This syndrome is the most striking evidence of pineal involvement in children having a tumor in this region. No favorable result has ever been obtained by organotherapy in patients with the pineal syndrome.

The pituitary gland is made up of two lobes. Two distinct hormones can be isolated from the posterior lobe. One of them, oxytoxin, produces tetanic contractions of the uterus. The clinical syndrome attributable to a deficiency of this hormone is unknown. The other hormone, vasopressin, raises the blood pressure and inhibits urinary secretion. It is probable that diabetes insipidus, often associated with lesions of the pituitary or adjacent structures, is caused by a lack of this substance, despite the fact that experimental and pathologic evidence on this point is contradictory. In any event, the antidiuretic action of this substance, which has been proved in normal persons, is of much value in relieving patients suffering from diabetes insipidus, whether or not this condition is due to pituitary dysfunction. This hormone may be administered subcutaneously, orally or by snuffing it into the nose.

The anterior lobe of the pituitary gland secretes two and probably three hormones. One of these, apparently produced by the acidophil cellular elements, controls normal growth. If the gland is destroyed by experiment in animals or by a tumor in children, growth is checked. The administration of large amounts of fresh tissue obtained from hypophysectomized animals is not followed by an increase in the function of growth. At times some improvement can be observed in pituitary nanism following oral administration of the gland. However, these patients have periods of spontaneous improvement, so it is difficult to be sure that the good results are due to glandular feedings. Injections of alkaline extracts of the anterior lobe into normal animals will in time produce gigantism and a condition approaching acromegally. However, the same extracts are not well tolerated by hypophysectomized animals, although growth may be temporarily stimulated.

Up to the present time it has been impossible to obtain a glandular extract that excites any physiologic activity in the human subject. After extraction with certain alkalis and acids, the residue of the anterior lobe still retains a hormone that causes precocious sexual maturity in young animals. A similar substance is excreted in the

urine of pregnant women. Its presence seems to serve as a test of some value for pregnancy. So far all attempts to relieve subjects with hypopituitary disturbances by the administration of this hormone have failed. On empiric grounds, thyroid extract has been used under similar condition without much success. Acromegaly is a disorder of growth almost certainly due to hyperactivity of the acidophil cells of the anterior pituitary lobe. For this reason glandular extracts seem contraindicated in its treatment. Curiously enough, the glycosuria that often accompanies acromegaly is frequently refractory to insulin therapy. In Putnam's opinion, the somnolence, mental dulness and obesity that often accompany certain types of pituitary tumors are caused by the interference of the neoplasm with functions of areas adjacent to the third ventricular rather than by glandular derangement. In such conditions, replacement therapy is of no value.

Abstracts from Current Literature

TUMORS IN THE PITUITARY AREA: THE NEUROLOGIC SYMPTOMS. THEODORE H. WEISENBURG, Arch. Ophth. **6**:589 (Oct.) 1931.

As the author states, "Knowledge of the symptomatology of tumors and of other lesions in the pituitary region has increased enormously in the last two decades, and the methods of diagnosis are such that, because of the information gained, first from the ophthalmologic and, second, from the roentgenologic standpoint, the general diagnosis of tumors in this area is comparatively easy. On the other hand, knowledge of the precise causes of the so-called endocrine disturbances, which at times are the sole manifestations of lesions in this area, has not advanced as rapidly, for while ten or more years ago it was customary to ascribe such symptoms to overactivity or underactivity of the anterior, middle and posterior lobes of the hypophysis, a great deal of doubt has been cast on such theories, and recently it has been the fashion to ascribe such symptoms to disturbances in the parts above the hypophysis, that is, in the walls of the third ventricle, in the hypothalamic region, the infundibulum and the stalk that connects the infundibulum with the posterior hypophysis. In fact, this tendency has been manifested to such an amazing degree that, while it is generally acknowledged that gigantism and acromegalia result from overactivity of the anterior pituitary lobe, there are some excellent investigators who ascribe the locale of this symptom complex to the hypothalamus." Experience reveals outstandingly that in the diagnosis of tumors in the pituitary area not only the pituitary gland itself, but all of the aforementioned surrounding structures must be considered. The sphenoid sinus, lying underneath the sella, from which adenomas occasionally are derived, should be included.

The author then discusses the functions of the pituitary area as indicated by experimental evidence. There is no doubt that the anterior lobe has two definite hormones, the first being concerned with the growth principle, and the second, with the sex principle. While hyperpituitary symptoms are distinct from hypopituitary, they have this in common: They produce demonstrable regressive changes in the reproductive organs, for in both there is an inhibition of the ovarian cycle.

The function of the posterior hypophysis is considered with that of the stalk, infundibulum and adjacent hypothalamic structures, for the reason that it is impossible to demonstrate clinically separate lesions of these separate structures. There is anatomic evidence of an interrelation between these parts; they have similar epithelial characteristics, and there is evidence that these cells represent the secretory principle which acts on all these inclusive structures. The infundibular lobe is a downward extension of the diencephalon, and there is a connection between certain nuclei in the walls of the third ventricle and the posterior and middle portions of the hypophysis. These groups of anatomic entities probably house ancestral mechanisms, common to all species, which have to do not only with the vegetative functions but also with primitive instincts, such as mating, satisfying hunger and thirst, restoration from fatigue by sleep, regulation of body temperature, self-protection by combat, etc. Furthermore, there is experimental and clinical evidence that the cerebral sympathetic centers are in the hypothalamus. Nonmedullated fibers have been traced to the spinal cord which connect with the abdominal and thoracic viscera, and there is evidence that some of these fibers connect with the anterior hypophysis itself.

Section 2 of the paper discusses the clinical evidences of pathologic conditions in the region of the third ventricle. The author states that compression in the area of the third ventricle is most important, and is sometimes caused by pituitary tumors. The walls of the third ventricle consist of the optic thalami on either side. As the thalamus is a sensory organ, lesions in this area may cause so-called central pains. As a result of lesions in the vicinity of the third ventricle there

are: disturbance in the sleep rhythm, usually hypersomnia; alterations in water metabolism, causing diabetes insipidus; disturbances in fat metabolism, and disturbances in growth and vegetative and emotional activities. If with hypersomnia there occur diabetes insipidus, adiposity and genital dystrophy, a lesion of the hypothalamic region should be suspected. On the other hand, primary hypophyseal tumors, not projecting into the third ventricle, may cause apathy and lethargy from lowered metabolism. Disturbance of the menstrual cycle in women and of the libido in men is the most common symptom in a pathologic condition of the anterior lobe. Headache is an early symptom and is usually frontal. Slight fatigability is common. Hypoplasia of the genital organs occurs in childhood, and an absence of secondary sexual characteristics in a person past the age of puberty. With the general inhibition of growth there are segmental deposits of fat in the abdomen, pelvis, shoulders, neck and breasts, the distal extremities appearing normal.

In the third part of the paper, the author discusses pituitary tumors. They may be divided into intrasellar and extrasellar. The intrasellar tumors are most often adenomas, which have origin in the glandular cells within the anterior lobe of the pituitary body. Histopathologically, they are: (1) the chromophilic adenomas associated commonly with a clinical picture of acromegaly; (2) the basophilic adenomas, a rare type, which are probably related to reproductive processes; (3) the chromophobic adenomas associated clinically with the hypopituitary syndromes.

A second type of intrasellar tumor is that of Rathke's pouch. These tumors are composed of epithelial cells often stratified and presenting rosettes into which cilia project from the cells of the buccal mucosa. The suprasellar tumors are tabulated as: adenomas, meningiomas, tumors of the craniopharyngeal duct, gliomas of the optic chiasm and aneurysms. These tumors give rise to the "chiasmal syndrome," primary optic atrophy, bitemporal hemianopia and a normal or relatively normal sella turcica, in contradistinction to the markedly enlarged and ballooned-out sella turcica in primary pituitary tumors. A table compares the pathology and symptomatology of all the various types found. The meningiomas occur in middle age and produce endocrine disorders rather late. The adenomas escaping through the diaphragm, cause mild hypopituitary signs, and are of more rapid course than the meningiomas. The craniopharyngeal duct tumors and adamantinomas, which are always suprasellar and often calcified, frequently cause secondary pituitary, hypothalamic symptoms and endocrine disturbances. Gliomas arise from the chiasm or the adjacent wall of the third ventricle and occur in young persons. Aneurysms are also included in this group of suprasellar lesions.

In a section on differential diagnosis it is pointed out that tumors of the pituitary may give rise to symptoms lesions elsewhere by direct extension into distant parts; or by extension through the ventricle system and through the aqueduct of Sylvius, causing midbrain symptoms; instead of a direct extension of the tumor, a generalized internal hydrocephalus may be produced, with dilatation of the lateral, third and fourth ventricles and attendant phenomena. On the other hand, tumors of the cerebellum frequently cause symptoms of dyspituitarism because of a secondary internal hydrocephalus, dilatation of the lateral and third ventricles and direct pressure on the pituitary region. In differential diagnosis, an adequate history of the progress of the symptoms is most important, for when lesions encroach on the pituitary area the corresponding symptoms appear late. These have been found in cases of generalized internal hydrocephalus in which a diagnosis could not be made before a postmortem examination. SPAETH, Philadelphia.

BIOLOGIC TYPES AMONG CRIMINALS. ERNST SEELIG, J. f. Psychol. u. Neurol. **42**:515 (June) 1931.

Seelig studies criminals as biologic and not as character types. He accordingly groups them as follows: 1. Criminals in whom the commission of crimes (regularly against property) is an occupation, the so-called professional criminals. This group

includes the "hold-up" man, the professional burglar, the vagrant who commits petty larceny, the prostitute who robs the men with whom she cohabits, and others. The only common characteristic of the members of this group is their general aversion to work; otherwise they represent the most varied types of personality.

2. Persons whose behavior in general is not antisocial and who are frequently industrious; nevertheless, they commit criminal offenses, usually against property. In this group are included the diligent but dishonest servant girl, the waiter who intentionally always makes errors in his favor in rendering the restaurant check and the "lady" from the higher social strata who "steals" a free ride on street cars. Other criminals in this group are the more serious offenders, such as the unusually efficient postoffice clerk who appropriates to himself letters containing valuables, the industrious store clerk who takes home many of the store's wares, etc. In contrast to the habitual criminals, who commit crimes because of their indolence, the persons in this group commit crimes because they possess very little or no inhibition. This group also contains various types of personalities.

3. The aggressive criminal. This group includes persons who, owing to their habitually bad temper, insult and assault, at the slightest provocation, persons with whom they come in contact. In this group belongs the quarrelsome peasant who, coming home intoxicated, abuses and even beats his wife and children. Many persons charged with homicide are also included in this group.

4. The sexual criminal. These persons commit various sexual crimes. They may commit sexual offenses during normal sex life or when engaged in sexual perversions (e. g., senile pedophilia and homosexuality). They possess one common characteristic, i. e., they are devoid of inhibition in their attempts to gratify their sexual desires — in contrast to some noncriminal persons who have similar sexual impulses and desires but who, because of the cultural, ethical and legal limitations of sex life, are able to and do inhibit their desires.

5. Crisis criminals. In this group are included persons who become embroiled in certain situations and conflicts from which they can escape only by committing some antisocial act. The crisis may arise from some external situation, such as in the case of an old maid who has found her lover late in life and who steals money from her employer to improve her lover's financial condition, or a young unmarried mother who kills her new-born infant; or the crisis may represent a subjective reflection of a critical phase in the endogenous development of personality, as when a lover kills his sweetheart and subsequently attempts suicide. According to Seelig, the crisis arising from external situations is regularly determined by subjective factors that depend on the peculiarity of the personality.

6. The affective criminal "in a narrow sense." Seelig characterizes the criminals in this group by adding the phrase "in a narrow sense," because the group does not include all criminals who commit offenses during affective excitement, but only those in whom the antisocial act represents biologically a motor discharge of an enormously increased affective tension. Not all affects are capable of provoking such a violent reaction. The affect is of the type ordinarily designated as "rage." Offenders whose criminal acts can be interpreted in this fashion are not numerous. Some of the cases of "homicide without premeditation" and "assault during a dispute" can be included in this category. Most of these persons have not the slightest idea of committing a crime before they actually commit it, and they are astounded at what they have done when they begin to realize the enormity and seriousness of the act. Seelig also includes in this group persons who, at the termination of normal sexual intercourse, commit various acts of violence, such as choking the partner in coitus; some of them even commit murder. These violent acts are then interpreted as motor discharges of an unusually increased sexual affect.

7. Persons who commit criminal offenses because of feeblemindedness. In these offenders there is an arrest of all inhibitory mechanisms, during which they utilize criminal methods to attain the goal of their strivings (primitive reactions). In this group are included the servant who sets fire to the employer's home so that

he may have a good excuse to stay away from work, and the discharged farm hand who, for revenge, sets fire to the farmer's household.

8. Persons who, owing to their distorted ideals and queer complexes, are convinced that it is their duty to commit an antisocial act in order to "improve conditions as they exist," and that in this way "mankind in general will be greatly benefited." Genuine criminals belonging to this group are rare.

Seelig points out that not infrequently a case may be encountered that may fit into several of these groups, and occasionally one that cannot be included in any of them. In spite of this, he believes that a classification such as he suggests, based on typical correlations between criminal behavior and the biologic reactions of the offender, affords a better visualization and a more genuine picture of the criminal population than the "bloodless" traditional classification of offenders into occasional, habitual, incorrigible, etc., types of criminals.

KESCHNER, New York.

BRAIN ACTIVITY OF THE SUCKLING. ALBRECHT PEIPER, Berlin, Julius Springer, 1928. Reprinted from Ergebn. d. inn. Med. u. Kinderh. **33**:504, 1928.

THE NEUROLOGY OF OLD AGE, THE GOULSTONIAN LECTURES FOR 1931. MACDONALD CRITCHLEY, Lancet **1**:1119 (May 23), 1221 (June 6), and 1331 (June 20) 1931.

The term "second childhood" is in current use among the laity to describe a set of phenomena occurring in an aged person which show many resemblances to those of early youth. The neurologist can push the homology still further and describe a condition not altogether unlike second infancy. Some time ago, the reviewer pointed out the necessity for the collaboration of neurologists in the study of these two extremes of life, and prophesied that more and more infantile reactions would be disclosed in persons of extreme age. These two interesting monographs could well be used as a starting point in the study. Both are well written, direct, well documented and equipped with extensive bibliographies.

Peiper's study takes the child through its first year after birth, but lays considerable stress on the unborn infant, its rhythmic activities, excitabilities and reflexes. Moreover, the author gathers together observations on premature infants, showing how certain responses are present which disappear even before the normal end of the gestational period. Defective children and anencephalic monsters are discussed, and some criteria for the recognition of deficiencies in the very young are indicated.

The new-born infant is equipped with a fairly complete sensory apparatus, but on the motor side is the equivalent of a midbrain preparation. The diencephalic centers would seem to be partially in operation. Nevertheless, the number and diversity of reactions are large and probably by no means exhausted in the author's treatise. The most striking reactions are the general reactions with which the child responds to any sharp stimulus. This nonspecific response later becomes more differentiated as the development of the brain progresses. A large section is devoted to the various tonic reflexes of labyrinthine, cervical and ocular origin, and to the postural reflexes, like those that have been observed in decerebrate animals. The author differentiates four types of movements: (*a*) athetotic movements, occurring only in premature infants, (*b*) reflex movements occurring in all children and (*c*) spontaneous, reflex-like movements occurring in mature and premature infants, disappearing progressively as (*d*) voluntary movements develop in the later months of the first year. Peiper looks on the third type as chain reflexes rather than as instinctive reactions. The appearance and later disappearance of such chain reflexes is well shown in the clutching reaction in the toes that is lost as the lower limbs come to be used for locomotion.

Psychologic aspects are considered at some length, but the author cautions against too liberal interpretation and disagrees altogether with the theories advanced by the psychoanalytic school. The higher centers are not yet developed in the

new-born infant, and it is quite improbable that impressions are laid down that may be resurrected at some later period in life. Comparative animal psychology meets with the same difficulties, and all conclusions are based on the thought processes of the experimenter rather than on those of the subjects experimented on.

Critchley's work is unusual in that it takes up the anatomic side first, then the neurologic side and finally the psychologic. Moreover, he finds himself constantly called on to decide whether the phenomena he observes are normal to senility, or whether there is something pathologic that occurs more frequently in old people than in others, but that is nevertheless nonspecific. The so-called senile plaques are a case in point. They occur in a large percentage of persons over 90, yet have been missed in centenarians and found in much younger persons. The author is against the opinion that dementia must inevitably occur on the basis of extreme years alone. Nevertheless, there are some rather typical changes that begin in later years and progress rather steadily to the end of life. Blunting of sensibility is emphasized, especially diminution and final loss of vibratory sensibility in the lower limbs. Amyotrophy without definite cause and reduction in the tendon reflexes are often observed in aged persons who are otherwise healthy. Most commonly observed are the extrapyramidal disorders, so commonly, indeed, that they are considered to be normal in old age. Hypertonia with loss of spontaneous movement is most common, sometimes rather strongly suggesting parkinsonism. Tremors are also common in the senium, and may appear in hereditary fashion. Much less common is athetosis or chorea, but restless movements, apparently spontaneous, yet lacking in purpose, are strikingly present in some persons. Critchley calls attention to the resemblance of these movements to those of the mentally defective child.

Definite senile neurologic syndromes, probably abiotrophies, are observed in the cerebellar ataxias, flexion paraplegia, etc., and probably the trophic alterations in the small muscles of the hands should come under this category. Lobar sclerosis, Alzheimer's disease and the chronic choreas are apparently not dependent on senility itself.

The psychologic aspects of senility are more easily subjected to satisfactory study than are those of infancy, but the terminal stages of senile dementia appear to be beyond reach. Several different types of alteration in the senile psyche are discussed, but there is much overlapping, and pure types are rare. Critchley calls attention to the need for better separation of the pure senile from the arteriosclerotic dementias, since so frequently there is a mixture of the two. Much remains to be investigated, since, as he says in his introduction: "The subject of old age has never been a popular one with the medical profession."

FREEMAN, Washington, D. C.

AMYOSTATIC DYSKINESIAS. E. HERZ, J. f. Psychol. u. Neurol. **43**:3, 1931.

Amyostatic disorders of motility differ from psychomotor disturbances chiefly by their more primitive structure; i. e., in the former the disturbances of motility affect a lower level of movement. They are purposeless motor discharges, intercalated into the entire motor capacity of the individual so that they interfere with rest by an overflow of innervation and a general disturbance of coordination and tonus regulation. This characterization of disorders of movement disregards the rôle played by the factors of volition and unconsciousness, even though most dyskinesias are involuntary phenomena.

For the proper differentiation of the various types of disordered motility Herz made most detailed cinematographic observations in a large series of various forms of dyskinesia. He studied in every case: (1) the effect of each individual movement, i. e., its direction and range of excursion as well as its structure and composition; (2) the direction of the movement, with special attention to its relation to volitional movements; (3) the change of movement, i. e., the relation of successive movements to each other; (4) the change of the time interval during which the

movement is executed, with special attention to the rhythm of the movement; (5) the tempo of each individual movement, and (6) the distribution of the dyskinesias.

In connection with these observations there were also investigated the changes in muscle tone, the effect of volitional movement on a given dyskinesia, the effect of a dyskinesia on volitional movement, tonic neck reflexes and associated movements.

Briefly, the author's observations may be summarized as follows: Every form of dyskinesia possesses certain definite characteristics that enable one to differentiate it from the other forms; this is true in most of the cases. From the point of view of alterations of motility, the dyskinesias may be divided into two large groups: (1) disorders of motility with varying changes of movement (chorea, ballismus, athetosis, torsions and the myoclonias); (2) disorders of motility with a uniform repetition of the same type of movement (tremor of the antagonists, myorhythmias, alternating to and fro movements and tics). As regards the interval between individual movements, the regular abnormal movements with rhythmic repetition of movement (tremor of the antagonists and myorhythmias) can readily be distinguished from the irregular forms of abnormal movement (chorea, athetosis, torsions, tics and alternating movements).

In chorea and ballismus the direction of movement corresponds fully to the proportionate continuous direction of a voluntary movement. In athetosis and torsions the direction of the movement is not continuous, owing to increases in tonus of longer or shorter duration. The myoclonias and tics are characterized by the lightning-like appearance and disappearance of the movements, whereas in tremor of the antagonists, in the myorhythmias and in alternating movements an abnormal movement is immediately associated with the recurrence of the same type of a movement.

A study of the structure of a dyskinesia reveals that the most complicated movements are gradually developed from the most primitive movements. In the myoclonias only parts of a muscle receive innervating impulses, so that actual movement is impossible. In chorea, athetosis and tics, individual movements are executed which appear in predominatingly greater numbers simultaneously in ballismus, torsions and in complicated tics. In the more complicated dyskinesias each movement can be seen to consist structurally of several individual movements.

It would seem that in these disorders of motility purposeful movements are not set into activity according to a definite design of movement and in accordance with the laws of synergy and coordination of movement, but that there is a more or less constant playful overflow of purposeless motor discharges either in the entire body or in an individual segment. The entire apparatus for the regulation of movement seems to be disintegrated and it cannot be checked; this gives rise to a loss of purposeful division of motor energy with a consequent inability to remain at rest. The appearance of a choreic person who exhausts himself during a "continuous storm of movement" is definite evidence of this irregular behavior of the motor apparatus. The various manifestations of the different types of dyskinesias are determined by the great variability of the respective disturbances of the different mechanisms subserving the orderly execution of purposeful movements. It is obvious that the manifestations of disordered motility must also be greatly affected by the functions of the mechanisms that still retain their integrity, as well as by disturbances of other functional components of the various apparatuses subserving motility in general.

KESCHNER, New York.

OBSERVATIONS ON CEREBRAL HAEMORRHAGE DUE TO CAUSES OTHER THAN ARTERIOSCLEROSIS. JAMES COLLIER, Brit. M. J. **2**:519 (Sept. 19) 1931.

In addition to arteriosclerotic causes of cerebral hemorrhage in all its forms, some twenty-four other causes are listed. They include: injury during birth or following trivial concussion; hemorrhagic pachymeningitis; oozing from blood vessels; increased permeability of vessel walls; diapedesis; encephalitis; polio-

myelitis; epidemic encephalitis; tuberculous meningitis; sinus thrombosis; venous bleeding; abnormal blood states; leukemia; purpura; infection with anthrax; insolation; neoplasms from the rupture of poorly developed vessels in a soft growth; aneurysm—infective in ulcerative endocarditis, puerperal infection, gonorrhea, etc., and occurring in coarctation of the aorta and also in polyarteritis acuta nodosa of Kussmaul and Dickson; the berrylike and often multiple aneurysms that have been termed congenital aneurysms. (Syphilitic aneurysms of the cerebral vessels seem not to give rise to hemorrhage, but berrylike aneurysms leading to hemorrhage are not uncommon in atherosclerosis.)

The frequency of both meningeal and intracerebral hemorrhage during the molding of the head in parturition is amplified and reference is made to the work of Mraczek, who found that some hemorrhage had occurred in one fifth of all the cases of stillbirth or death within three months of birth. The oozing of blood from vessels owing to increased permeability of the walls is not considered common by the author; he thinks that the presence of an aneurysm is more probable in such cases.

Hemorrhage in encephalitis and poliomyelitis is next considered; in regard to the latter, Collier concludes that these conditions do not seem often to cause major hemorrhage, either meningeal or cerebral. Hemorrhages within the cranial cavity may cause symptoms resembling encephalitis in many respects, and it is sometimes difficult to make a differential diagnosis. Hemorrhage in encephalitis may occur, but it is not frequent. Neoplasms of soft texture are important causes of cerebral hemorrhage, and a sudden increase in the severity and multiplicity of symptoms in cerebral tumors may be due to hemorrhage.

Considerable space is given to a discussion of cerebral aneurysms. They may give rise to the most varied clinical syndromes. At least one fifth of the numerous specimens in museums have been discovered by chance at necropsy, according to Collier. The statement is made that they are never of syphilitic origin; some are known to be definitely of infective origin, and probably the majority have an infective etiology. Some may be of the so-called congenital type. Many never rupture or give rise to any symptoms; many that leak heal permanently and become obsolete. When an aneurysm clots in part or when its wall calcifies, then and then only does it give rise to local pressure symptoms, and it does so most commonly in the region of the optic chiasma causing a syndrome indistinguishable from that of a pituitary tumor. The author states that such a picture followed by signs of cerebral hemorrhage can be due to nothing other than aneurysm. In aneurysms that rupture slowly and leak rather than burst, there is a great tendency for the rupture to heal locally and for another to occur later in another part of the sac, perhaps in another part of the brain or its covering.

Hemorrhage from an aneurysm may be of the following types: (1) transdural, (2) subdural, (3) subarachnoid and (4) intracerebral rupture, (5) primary rupture into the ventricle and (6) rupture of an internal carotid aneurysm into the cavernous sinus.

In regard to treatment, Collier believes that it is always advisable to drain freely and repeatedly so long as symptoms of increased intracranial pressure persist. In cases of cerebral hemorrhage, increase of intracranial pressure is always the cause of death, and surely, concludes the author, it is wise to keep this within bounds by draining whenever it is possible to do so.

FERGUSON, Niagara Falls, N. Y.

THE QUESTION OF IRON IN DEMENTIA PARALYTICA ON THE BASIS OF COMPARATIVE HISTOPATHOLOGIC INVESTIGATIONS. F. WERTHAM, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:62 (Sept.) 1931.

Iron has been demonstrated in the brain in dementia paralytica by Lubarsch and Spatz. It is found as iron granules lying free in the adventitial space of the small vessels, in the adventitial cells, in the microglia, and throughout the entire nervous system. This iron has come to be looked on as a specific feature of

dementia paralytica. It has been found in this distribution in no other disease of which one knows. Lubarsch has gone so far as to say that the iron in dementia paralytica is a more constant factor than the mantle of plasma cells about the vessels. Wertham says that, while in many cases of dementia paralytica one must search for plasma cells, the iron reaction generally is prominent. The presence of iron has not been sufficiently investigated in the long-standing cases of dementia paralytica, but it is possible that in these cases it is of great diagnostic value.

While the ingestion of iron in dementia paralytica represents a specific condition par excellence in the nervous system, there are several factors regarding it which remain obscure. Is the process a permeability phenomenon; is it a destructive process with transportation to or away from the vessels, and to what extent is it related to the inflammatory processes of the disease? Furthermore, what is the relation of ingestion of iron in the microglia cells to proliferation of the microglia? Thus far "Paralyseeisen" has been looked on as specific in dementia paralytica.

Wertham reports iron in the brain of a hen. He investigated the material from thirty-five hens that had been inoculated with Spirochaeta gallinarum. This parasite produces changes in the brain, meninges and choroid plexus, as well as elsewhere in the body. Wertham was able to demonstrate iron in the brains of these animals by Spatz' quick method, as well as by the Turnbull blue technic. In many cases the adventitial sheaths of the small vessels contained iron. Less iron was found in the glia cells, and here it was always in the microglia. In other glia cells it was practically never seen. The iron found in these brains was widespread. It had nothing to do with softening and was not related to vascular proliferation. It was found chiefly in the frontal lobe, and in smaller amounts in the cerebellum, chiefly in the vascular sheaths of the molecular layer. Iron could be demonstrated in the meninges, although little was found in the spinal cord. The distribution of the iron was similar to that described by Spatz in dementia paralytica. Histologically, the process appeared to be similar to that of dementia paralytica. Plasma cells were found in the brain and meninges. The microglia cells showed proliferation in numbers, and in some cases pronounced microgliosis with rod cell formation. The microgliosis was in some cases pronounced, in others less marked. Changes in the ganglion cells, glial foci and hyperemia were found.

Three symptoms stand out: iron in the brain, the proliferation of the microglia cells and plasma cells. All these features are characteristic of dementia paralytica. Another feature is the presence of spirochetes in the brain, an observation which is constant in animals killed early in the disease.

Thirteen control hens showed the same distribution of iron in the brain as that found in the hens inoculated with the spirochetes.

So-called "Paralyseeisen" occurs spontaneously in hens among other pathologic changes characteristic of dementia paralytica. Spatz has been unable to find this iron in any other encephalitides of animals; that is, Borna's disease, distemper and experimental trypanosomiasis.

ALPERS, Philadelphia.

THE NEUROLOGICAL COMPLICATIONS OF SERUM TREATMENT, WITH A REPORT OF A CASE. I. M. ALLEN, Lancet **2**:1128 (Nov. 21) 1931.

Neurologic complications of serum disease are uncommon. During the forty years since this form of therapy was instituted, less than fifty cases have appeared in the literature.

A case is presented in which 10 cc. of antiscarlet fever serum was given to a man, aged 22, who had a typical attack of scarlet fever. On the twelfth day following the injection of the serum, serum sickness developed; two days later paralysis supervened, which was most pronounced in the right deltoid and, to a lesser degree, also affected the spinati and serratus magnus. It was accompanied by spontaneous sensations, which were evidently of radicular origin, and by an impairment of sensation over an area corresponding to the distribution of the

fifth cervical sensory root. Pains, also apparently of a radicular type, appeared about the left shoulder, but disappeared without the development of any motor disability. Pronounced wasting of one of the affected muscles was a prominent feature. Recovery was gradual and independent of any local treatment.

The clinical picture was evidently that of radiculitis affecting chiefly the right fifth cervical root, but also involving to a minor degree one or two sensory roots below that level, as well as sensory roots on the left side. The relation of the condition to the serum was evident and was identical with that of other cases described in the literature, although in this case subjective sensory disturbances were less obvious and the objective sensory changes were more pronounced.

The clinical course of these patients usually follows a general type. About eight days after the injection, typical serum sickness develops, with pains in the limbs and joints and, in some instances, headache and vomiting. After an interval of from two to five days the pains become severe, intermittent and stabbing, localized in some cases in both upper and lower limbs, in others in the distribution of a peripheral nerve, but in most cases in one or more segmental areas. The pain continues in a severe form for from two to four weeks. In most cases muscular weakness and atrophy appear early, and the reflexes in the corresponding segments are diminished or entirely disappear. Electrical reactions may be altered. Objective sensory changes are usually slight and transient. Occasionally, muscular weakness is not discovered until the patient tries to work. Complete recovery takes place in from one to eighteen months, except in a few cases in which slight residual weakness and wasting persist.

These neurologic complications may be classified in four groups: (1) a radicular type, resembling an Erb-Duchenne paralysis of acute onset; (2) a neuritic type, in which single nerve trunks are affected; (3) a polyneuritic type, in which the clinical picture resembles that of toxic polyneuritis, and (4) a cerebral type in which symptoms and physical signs probably resulting from intracranial pressure or cerebral edema are the prominent features.

It is doubtful if any one pathogenesis can explain all cases. Local and general edema would explain the cerebral cases and the paralyses of single nerves, while radiculitis, either from local edema or inflammation at the exit of the nerve roots from their dural sheaths, appears to be the most reasonable explanation for the amyotrophic and polyneuritic cases. The appearance of the symptoms and physical signs from two to five days after the onset of serum sickness, when both the urticaria and the meningeal reaction are most pronounced, suggests strongly that either a local edema or the meningeal reaction is the source of the local condition. There is a suggestion, too, that these clinical features may appear independent of external manifestations of serum sickness.

BECK, Buffalo.

ANGIOMATOUS TUMORS OF THE NERVE CENTERS. G. ROUSSY and C. OBERLING, Presse méd. **38**:179 (Feb. 5) 1930.

The angiomatous tumors of the central nervous system, while rare, have been known for a long time. Lechner, in 1922, was able to gather fifty-six cases. Lindau called attention to them in 1926. He believed that most of the cerebellar cysts, notably those of the cerebellar lobes, are due to angiomas, which are often so small as to escape notice. Often these cysts are associated with angiomatosis of the retina, known as von Hippel's disease. Similar tumors can be found in the medulla and cord, where they often form cavities resembling syringobulbia and syringomyelia. They may be found, too, in other viscera. It is justifiable to speak of the entity described by Lindau as Lindau's disease. Lindau looked on the cells in these tumors as of endothelial origin; so, too, did Cushing and Bailey, who recognized three groups of angiomas: cavernous, capillary and cellular. Roussy and Oberling claim that there are only two: cavernous and reticulo-endothelial.

The cavernous type they describe is similar to that type as depicted by others. They report two cases, one found in the peduncular region and the other in the

region of the cornu ammonis. The reticulo-endothelial type is found in the cerebellum, medulla and cord. In every tumor of this type there are large vessels, which represent the nourishing vessels. From them radiate vessels of varying size that reunite by a system of extremely delicate capillaries which are lined by flat endothelial cells. Roussy and Oberling have seen red and white cells in the lumen of these vessels, as well as erythroblasts and myelocytes. The tissue among the vessels is formed by cells with a round nucleus and with numerous cytoplasmic extensions. These cells are attached to the walls of the vessels or anastomose with one another, forming reticular spaces among the vessels. Among them are often seen xanthomatous cells filled with fat. Reticulin can be demonstrated among the cells. Roussy and Oberling propose the name angioreticuloma for these tumors, sheathed as the tumor cells are by a reticular space, demonstrated by the character of the cells, the presence of reticular fibrils and xanthoma cells. In many regions of these tumors the reticular cells are transformed into fibroblasts, a process first described by Maximow. The xanthomatous cells can develop also from the perivascular reticular cells.

Cyst formation is an important part of these tumors. Sometimes they are minute; sometimes they occupy the entire extent of the tumor. Some tumors are entirely solid. Roussy and Oberling say that the cysts are not mere degenerative cysts. The cyst cavities are formed by the accumulation of plasma in the meshes of the reticular tissue or in the cerebral tissue in contact with the tumor. The cavity distends little by little, destroying tumor tissue, and as it approaches the cerebral tissue a wall of gliosis forms. Histologic study confirms the fact that the cysts are formed by a process of exudation. Roussy and Oberling explain the absence of cysts in some tumors by the fact that if the tumor is in communication with a perivascular lymphatic, cerebral or meningeal, drainage of the exudate follows and no cyst formation ensues. The cyst formation can take place also in the adjoining brain tissue. Angiogliomas have a structure similar to the angioreticulomas, but the intervascular cells are not of the reticular, but of the glial, series.

ALPERS, Philadelphia.

PATHOLOGY OF SPINAL DISEASE IN AFFECTIONS OF THE VERTEBRAL COLUMN. CTISAKU KOBAJASHI, Jahrb. f. Psychiat. u. Neurol. **48**:13 (May 15) 1931.

In a man, aged 72, severe pain developed in the vertebral column. Roentgenologic examination revealed considerable alterations of the lumbar vertebrae, especially of the first. Although the roentgenologic signs were not of the type ordinarily associated with endospinal disease, nevertheless the possibility of a conus lesion had to be taken into consideration. Very shortly after the onset of pain in the spinal column, weakness in both lower extremities suddenly developed, with spasticity and bilateral pyramidal tract signs. During the next two years there were several variations and remissions in the signs and symptoms, and five years later there appeared slight disturbances of bladder function but no objective sensory changes. At about the same time there set in a definite limitation of movement of the vertebral column, and the pyramidal tract signs in the lower extremities became more marked. Not until the following year, the sixth of the illness, was there any evidence of sensory involvement, and even then the objective signs of this involvement were unusually slight. The upper extremities remained unaffected throughout. The patient remained in this condition during the next two years, at the end of which he died, at the age of 79, from bilateral lobar pneumonia.

The peculiar clinical course of the disease, the sudden onset of spasticity, instead of flaccidity, of the lower limbs and the series of remissions for two years, followed by a continuous progression of symptoms with a paucity of objective signs of sensory disturbances presented great difficulties in the differential diagnosis between disseminated sclerosis, spinal cord tumor and spondylitis with secondary disease of the cord.

Necropsy and histologic examination revealed: plastic leptomeningopathy (massive thickening of the leptomeninges, which were in some areas adherent to

the spinal cord) and marginal degeneration of cord tissue, which was most marked in the lowest portion of the cord. In this marginal degeneration the dorsal portion of the cord was mostly affected, but as the process ascended this portion of the cord seemed to have been affected less and less, and as the cervical region was reached the brunt of the process was found in the ventral portion of the cord where it assumed the appearance of a diffuse transverse lesion. In addition to this purely degenerative (abiotrophic) process of the myelin sheaths, there was a vascular degenerative process — a severe chronic disease of the vessel walls, more marked in the caudal than in the oral portion of the cord. The white substance was more affected than the gray, and the posterior horns more than the ventral. No evidences of an inflammatory process were seen, but the presence of evidences of recent destruction of myelin suggested that the process had not run its course and was still in progress at the time of death.

Kobajashi believes that the case is one of pure degeneration of the cord, in which the disease of the vertebral column was most probably the primary causative factor. The spondylitis gave rise to a pachymeningitic process, which exerted its deleterious effects on the cord in two ways: (1) by direct pseudocompression of the cord proper by the tumor-like meninges; (2) by interfering with the circulation of the cord (*a*) by compression of the vessels and (*b*) from the senile changes in the vessels themselves.

KESCHNER, New York.

TREATMENT OF POLIOMYELITIS. E. B. SHAW, H. E. THELANDER and M. A. LIMPER, J. A. M. A. **97**:1620 (Nov. 28) 1931.

Shaw, Thelander and Limper report the results of treatment of a series of 104 patients with poliomyelitis. Specific therapy was attempted in ninety-two cases. Of fifty-three patients treated before the onset of paralysis, twenty-eight showed no paralysis at any time, fifteen showed transient weakness, which had entirely disappeared before dismissal, nine showed persistent paralysis and one died. The average age of the unparalyzed patients was 9½ years; of the transiently paralyzed, 10 years, and of those with definite paralysis, 17 years. This is at least significant to the hypothesis that better results are obtained in the lower age group. The average spinal fluid cell count was 146 in the unparalyzed group, 119 in the transiently paralyzed group and 197 in the persistently paralyzed group, 270 in the single fatality. These averages were made up from widely varying individual cases and, the authors believe, are without significance. Serum was applied, on the average, 2.7 days after onset of symptoms in the unparalyzed group, 3.6 days in those with transient paralysis and 3.4 days in those with persistent paralysis. The average amount of serum used in the group treated preparalytically was, respectively, 120, 151, 209 and 375 cc. In the group treated in the acute stage after the appearance of demonstrable weakness, of thirty-nine patients, nine showed transient weakness; twenty-three persistent paralysis, and seven died. The average age in those with transient weakness was 6.8 years; 11.7 years in those with persistent paralysis, and 19.8 years in the fatal cases, again showing the higher average age in those with serious outcome. Average cell counts were 67 in the transiently paralyzed, 194 in those with persistent paralysis and 199 in the fatal cases. Treatment was instituted on the average of 3.7 days after onset of symptoms in the transiently paralyzed, 4.2 days in the cases of paralysis and 6.3 days in the fatal cases, coinciding with the general idea of the importance of early treatment. The transiently paralyzed patients received an average of 84 cc. of serum or plasma, the permanently paralyzed 156 cc., and in the fatal cases 156 cc. was given. Of the fifty-three patients treated before the onset of paralysis, 83.4 per cent showed no permanent paralysis; 16.9 per cent showed definite persistent paralysis, and 1.9 per cent died. Of the thirty-nine patients treated after the onset of paralysis while the disease was still acute, 23.08 per cent showed no end paralysis, 59 per cent showed definite paralysis and 18 per cent died. It is unfair to attempt to compare the results in these two groups of cases. While the first group included at least a few benign cases, the second group included many extremely virulent cases referred to the hospital because of their fulminant course. Such a series of cases

is far from being a conclusive answer to the problem of treatment of poliomyelitis; it seems, however, fairly convincing evidence of the value of such treatment. To have watched these patients one by one was far more convincing than a statistical report can possibly show, even if one discounts the enthusiasm which must inevitably attend the pursuit of such a problem. It is the authors' conviction that the use of known highly immune serum will be productive of consistent results and that hyperimmune animal serum offers the greatest promise in this direction.

EDITOR'S ABSTRACT.

SYPHILITIC SUBARACHNOID HEMORRHAGES. MICHAEL KAMIN, Jahrb. f. Psychiat. u. Neurol. **48**:1 (May 15) 1931.

In a woman, aged 60, affected with extensive neurosyphilis, a meningeal syndrome developed suddenly which terminated fatally at the end of one week. Necropsy revealed a subarachnoid hemorrhage, with bloody extravasation at the base of the pons, cerebellum and convexity of the brain. Microscopic examination showed an usually severe generalized syphilitic involvement of the walls of the blood vessels.

The histologic features in the brain were those of a primary disease of the walls of the meningeal vessels and not of a reaction to the hemorrhage. The vessels showed definite evidences of endo-arteropathy and, in some areas, slight evidences of periarteritis. The meningeal infiltrates not only involved the perivascular spaces, but were diffuse and so dense in some areas that they formed knoblike nodules. The vessels in the brain itself also showed endo-arteritic and periarteritic changes, so that the entire pathologic process was that of an endo-arteropathy associated with meningovasculitis. No aneurysmal ruptures were detected to account for the extravasation of blood. One must therefore think of the possibility of hemorrhage due to diapedesis, of the same type that occurs in so-called idiopathic subarachnoid bleeding. Various theories have been invoked to explain in these cases the bleeding by diapedesis. Of these the theory advanced by Pollak and Rezek appears to Kamin to be most acceptable. These observers believed that such bleedings must always be preceded by actual disease of the vessel wall. The primary condition of the vessel, however, is not the sole cause of the hemorrhage, so that just prior to the latter there must supervene some other "acute" factor. This factor may vary; it may be in the nature of possible metabolic disturbances or of an abnormal reaction in the brain tissue itself. This "acute" factor (?) leads to injury or destruction of the endothelial cells of the intima, which increases the permeability of the vessel wall. In this manner the blood stream is diverted either into the interstices in the vessel wall itself — intramural bleeding — or into the perivascular tissues. There is no doubt that the cause of this "acute" damage to the endothelium must be sought in the circulation.

In the case reported in this communication, severe involvement of the intima with destruction of the endothelial cells was actually observed. The remaining walls of the vessels also showed marked alterations, such as coarse connective tissue proliferation, infiltrations, edema and local necrosis with splitting of the vessel walls. It may thus be assumed that in the presence of such marked changes in the vessel walls, hemorrhagic extravasation occurred into the surrounding tissues as soon as the protective endothelial lining became permeable. In this connection the author points out that the patient in this case had been suffering from severe enteritis during the last years of her life. He suggests the possibility that the intestinal toxins from the enteritis may have affected the endothelium of the intima in the meningeal vessels the walls of which had already been severely injured by syphilis, so that diapedesis could readily occur.

KESCHNER, New York.

ON THE CHEMICAL NATURE OF PELLAGRA TOXIN AND THE THIOSULPHATE TREATMENT OF PELLAGRA. IBRAHIM SABRY, Lancet **2**:1020 (Nov. 7) 1931.

It has been proved that vegetable pigment is indistinguishable from tyrosine (oxyphenylalanine). This substance in the presence of a specific ferment, oxydase,

changes to a colored end-product. A similar process has been observed in the ink-fish. Furth and Prizbram have found a specific ferment in the ink glands of this fish called tyrosinase, which has the power of changing the colorless tyrosine, an intermediate product of metabolism, to a substance first orange-red and then black. Hence there are two important factors essential for the manufacture of pigment, first, a mother substance of the phenyl group, allied to tyrosine, and finally, a specific ferment (oxydase) which oxidizes this uncolored substance to a colored end-product. Furthermore, the author allies himself with Bloch in the belief that human pigment (melanin) is also formed from a mother substance by the action of a ferment.

From these conclusions a view is formulated by Sabry as to the chemical nature of pellagra toxin. Pellagra is a toxemia; the characteristic pigmentation is an invariable concomitant of the disease. Therefore, the toxin of pellagra, be its origin what it may, must be related to the hyperpigmentation. It must be the initiator of the extra pigmentation and cannot differ materially from the mother substance of the pigment itself. The author is opposed to the current view that the causal factor of pellagra is a vitamin deficiency. He proposes that pellagra might be caused by an excessive ingestion of maize or beans, the latter unquestionably containing a considerable amount of the pigment-forming ferment.

Apparently, a number of persons with pellagra were treated with sodium thiosulphate, but the paper is weakened because no clinical data are detailed. The author uses this drug because it is a powerful parasiticide and germicide. He injects daily 10 cc. of a 10 per cent solution of sodium thiosulphate sterilized in an autoclave. The number of injections required varies, according to the severity of the case, from twenty to sixty. There are neither complications nor contraindications.

The lesions in the skin are aborted in the early cases after a few injections, and disappear very quickly in the late and lingering cases, instead of lasting a whole season or even a whole year. It is gratifying to note the quickness with which the gangrenous limbs (sometimes occurring as a late manifestation of this disease) completely heal. The diarrhea, which is a very persistent and most distressing symptom, and which does not easily yield to any form of treatment even in early cases, stops altogether after a few injections. In the advanced cases, a distinct amelioration occurs. After a few injections the number of stools decreases from twelve or even twenty to four or six a day. The gastric symptoms cease before the treatment is over. Marasmus, insomnia and melancholia, when present, soon improve, and patients who doubtless would otherwise have died, not only survive, but recover.

BECK, Buffalo.

PSYCHOCHEMISTRY: SOME PHYSICOCHEMICAL FACTORS IN MENTAL DISORDERS. WALTER FREEMAN, J. A. M. A. **97**:293 (Aug. 1) 1931.

Freeman states that the application of another of the fundamental sciences to the study of behavior, namely biochemistry, is being witnessed today, and the designation psychochemistry is the natural result. Advances in a science emanate from those who, already versed in two different disciplines, work in the field of knowledge lying between them. Mere collaboration of two different experts will not be so productive, since neither can be completely in sympathy with the point of view of the other. Few biochemists are versed in psychiatry, however, and few psychiatrists have more than a bowing acquaintance with such terms as colloidal dispersion, interfaces, ionic dissociation and oxidation-reduction. Psychochemists, therefore, will be grounded in biochemistry as well as in psychiatry and will investigate the problems of normal and abnormal behavior from the standpoint of altered chemical reactions in that master tissue of the body, the central nervous system. The failure of microscopy to demonstrate structural alterations in the so-called functional psychoses is driving the investigator into new channels of research. The results of this activity are just beginning to appear and will grow tremendously in volume. What future accomplishments may be witnessed are

beyond human power to foretell. Dementia praecox, manic-depressive psychosis, paranoia and epilepsy represent four groups of disorders that rest on no constant, well defined alteration in the histology of the nervous system. None can doubt, however, that there exists an underlying structural deviation, provided such a definition is pushed to its logical limits to include molecular and ionic imbalances. Probably the changes are much more gross than that and will be readily demonstrable when proper methods are applied. Such work as that already performed is sufficient to enable one to erect hypotheses concerning the probable underlying physicochemical mechanisms concerned in some of these major abnormalities. Most clearly indicated is the rôle of water balance in epilepsy, although this also involves such mechanisms as hydrion concentration, oxidation-reduction and salt equilibrium. Moreover, the rôle of defective oxidation in the nervous system in schizophrenia also rests on considerable evidence, and the striking parallels, from the chemical standpoint, between the phases of manic-depressive psychosis and the hibernation cycle of certain mammals, point to some phasic alteration in colloidal dispersion and electric potential. In view of its newness the author makes a survey of the field, and the possibilities of its further development. He emphasizes that there are certain biochemical processes associated with disorders of behavior, and that if one is equipped with a knowledge of their workings one may be able, by supplying deficiencies, by preventing excesses, by controlling periodic shifts in various equilibriums, to bring about artificially conditions that approach the normal. The psychochemist has a large order.

EDITOR'S ABSTRACT.

AMYOTROPHIC LATERAL SCLEROSIS (A CLINICAL AND PATHOLOGIC CONTRIBUTION). P. OTTONELLO, Rassegna di studi psichiat. **18:** 221 (May) 1929.

The author reports in detail eleven cases of amyotrophic lateral sclerosis from the clinical standpoint and five from both the clinical and the pathologic standpoints. He pays particular attention to the etiology and pathogenesis of the clinical manifestations. He is opposed to any narrow limitations or distinction of amyotrophic lateral sclerosis from other bulbospinal spastic and trophic clinical syndromes, as transitory stages are frequently found that point to a strict relationship between lesions of the cells of the anterior horn and of the medullary pathways. Among the various conclusions that the author reaches, the following are worthy of consideration: (1) The lesion of the pyramidal tract as well as of the cells of the anterior horn has the definite characters of a primary process. (2) The perivascular infiltrations that are occasionally found are so slight as to be considered secondary to the process of disintegration.

A study of the lesions that are found in the cells of the anterior horn and in the medullary pathway leads to the consideration that amyotrophic lateral sclerosis is a pathologic condition, the pathologic substratum of which consists fundamentally of the association of lesions involving the two neurons of voluntary motility. Such facts, however, do not authorize a separation from the pathologic standpoint between amyotrophic lateral sclerosis and other pathologic conditions in which the lesions are predominantly or exclusively circumscribed in one of the two systems, not only because of the close analogies of the elementary lesions in these various diseases, but because of the frequency with which one observes histologic pictures of transition between the various pathologic conditions mentioned. The author believes in the systemic nature of amyotrophic lateral sclerosis, and considers the lesion of the central and peripheral neurons as being independent of each other; therefore, he does not subscribe to the opinion of Bertrand and Bogart of an early involvement of the synapses between the two neurons.

On the question of pathogenesis, the author develops extensively his own conception of the vulnerability of the various structures of the spinal cord on the basis of a difference in chemical structure. The predisposing and determining factors of the disease are also studied from a biochemical standpoint. From the etiologic standpoint, the author emphasizes the importance of toxic and infectious diseases, among which syphilis seems to play an important rôle.

FERRARO, New York.

THE CONDITION OF THE VEGETATIVE NERVOUS SYSTEM IN EXOPHTHALMIC GOITER AND IN THE BASEDOWOID SYMPATHETIC SYNDROME. M. LABBÉ, E. AZÉRAD and E. SOLOMON, Ann. de méd. **29**:271 (March) 1931.

Exophthalmic goiter is a combination of two different syndromes: (1) hyperthyroidism, and (2) a disturbed balance of the sympathico-vagus systems with predominance of sympathetic excitability. Both syndromes may occur isolated; in the first case in the form of goiter with hyperthyroidism, in the second case in the form of the "basedowiform" syndrome. The classic test for the demonstration of hyperthyroidism is the determination of the basal metabolic rate. The Goetsch test and the oculocardiac tests, however, devised for the examination of sympathetic and vagus functions, do not always give uniform results.

The following method was described to determine the degree of excitability of the vagus: The patient rests on a couch and his pulse rate is counted; the number obtained is an expression of the "relative tonus," the equilibrium between sympathetic and vagus regulation of the heart. Then 0.5 mg. of atropine is injected intravenously. The pulse rate is increased after the injection, still more so if the patient stands erect (orthostatic reaction). After lying down again, the pulse becomes slower. If the rate is approximately the same as it was before the patient stood up, the experiment is finished. If, however, the pulse rate is rapidly diminished again, the paralysis of the vagus has not been complete. Another 0.25, 0.3 and, finally, 0.75 mg. of atropine are injected at short intervals, until the patient's pulse rate does not slow down below the rate observed after the injection. The rate in the prone position is indicative of the "absolute tonus" of the sympathetic; the difference between the value for the latter and the pulse rate before the injection indicates the "vagus tonus." According to Danielopolu, the following rates are averages for normal persons: relative tonus, 72; absolute vagus tonus, 52 (from 48 to 58); absolute sympathetic tonus, 124 (from 116 to 128).

Of nine cases of exophthalmic goiter an increased irritability of vagus and sympathetic (amphotonia) was found in seven. Relative tonus from 88 to 120; absolute vagus tonus from 44 to 72; absolutely sympathetic tonus from 104 to 188. From 1.25 to 1.75 mg. of atropine was used. In three cases of toxic adenoma, the corresponding figures were: from 80 to 88; from 24 to 48, and from 112 to 132. In the first group the oculocardiac test was normal in three cases; in three other cases the pulse rate was reduced during compression of the eyes.

WEIL, Chicago.

MENINGOCOCCIC (LATER ALSO STAPHYLOCOCCIC) MENINGITIS, LOW SPINAL SUBARACHNOID BLOCK, ABSCESS, LAMINECTOMY, RECOVERY. J. H. ARNETT, M. Clin. North America **13**:1051 (Jan.) 1930.

Only once before has a case of meningococcic meningitis followed by a staphylococcic infection been reported; this was by Osler in 1899. Arnett's case, therefore, is a rare one; although secondary infection of the meninges is not uncommon, it is generally due to the pneumococcus. In Arnett's case, the patient, a boy aged 14, had an attack of meningococcic meningitis with all the usual clinical and bacteriologic evidences of that disease. He seemed to be doing well following intensive treatment with serum until the eighth day, when the temperature began to rise again and he complained of generalized pains. At the same time, strabismus, optic neuritis and rigid retraction of the neck developed. On the eighteenth day, a combined tap was done, and both lumbar and cisternal fluids showed a growth of Staphylococcus aureus. Ten days later, evidence of block appeared — lumbar pressure could not be elevated by the Queckenstedt maneuver, whereas pressing on the jugular vein caused a prompt rise in cisternal pressure. Objective examination and visceral symptoms localized the lesion at the second lumbar root of exit, and a laminectomy was performed. An abscess containing about 40 cc. of pus and a mass of matted cauda equina roots was found centrally in the dural sac at the

level of the third lumbar vertebra. This was opened and drained, and the patient improved steadily, leaving the hospital on the twenty-seventh day after the operation almost entirely well.

Arnett considers that the optic neuritis in this case was not due to intracranial pressure but was rather a perineuritis of the optic tract representing an inclusion of the optic nerve meninges in the general meningitic process. Another unusual feature of this case was the appearance of the obstruction at the widest portion of the subarachnoid space, instead of, as is usual, at the narrowing due to the cervical or lumbar enlargements. Arnett advises keeping in mind the possibility of the formation of an abscess and block at the lowest portion of the subarachnoid space. A diagnosis must be made by comparative spinal manometry and careful neurologic study, and not merely on the basis of hyperesthesia and pain in the lower extremities. Because of the excellent outlook if the abscess can be localized and drained, recognition of this condition is of much practical importance.

DAVIDSON, Newark, N. J.

ON THE PERMEABILITY OF THE MENINGEAL BARRIER IN PATIENTS WITH MENTAL DISEASE DURING HYPERTHERMIA AND WITH EXPERIMENTAL ASEPTIC MENINGITIS. C. E. ROBERTI, Rassegna di studi psichiat. **20**:682 (July-Aug.) 1931.

Starting from the fact that the Flatau test for the meningeal permeability (acid fuchsin test) is positive in pathologic conditions of the meninges, especially inflammations, though according to the author himself the results are negative in dementia paralytica, Roberti has experimentally reproduced aseptic meningitis in patients suffering from schizophrenia or from syphilis of the central nervous system through the injection into the vertebral canal of 1 cc. of a colloidal suspension of silver. In another group of patients he injected intravenously some antipyogenic vaccine in order to produce hyperthermia, and finally, in a third group of cases, he studied the permeability of the meninges during the malarial paroxysms.

1. The result of the investigation is that in experimental hyperthermia produced by the intravenous use of antipyogenic vaccine the data have been negative for the passage of the chromogen of the acid fuchsin into the cerebrospinal fluid, notwithstanding a previous extraction of fluid with the intent of establishing a drain that might favor the exchange between the blood and the cerebrospinal fluid.

2. In malarial hyperthermia in the course of dementia paralytica the resistance of the barrier to acid fuchsin is unchanged, the chromoneuroscopic test always giving negative results.

3. Experimental aseptic meningitis does not provoke a modification of the barrier analogous to that of the common type of meningitis, and especially of the tuberculous one, in which the chromogen from the blood passes into the cerebrospinal fluid.

4. Positive results are reported in only two cases of terminal dementia paralytica in which aseptic meningitis was experimentally provoked, which might be explained on the basis that the experimental meningitis enhances the leptomeningeal process of dementia paralytica.

5. Aseptic experimental meningitis is an experimental condition of brief duration and is without danger to the patients.

FERRARO, New York.

THE INTRACAROTID METHOD OF TREATMENT FOR MENINGITIS WITH RECOVERIES. JOHN A. KOLMER, J. A. M. A. **96**:1358 (April 25) 1931.

Kolmer believes that, while the intracarotid route of medication has not solved the treatment of septic meningitis, yet it has proved a safe and clinically applicable procedure offering some hope and advantages over ordinary intraspinal methods of treatment. When combined with cisternal or spinal drainage and medication, it appears to bring antibacterial agents into more widespread and intimate contact

with the infected meninges than is possible by intraspinal medication alone. It is therefore an improvement in the route of medication, although ultimate success must await the production of more therapeutically active immune serums and specific chemotherapeutic substances than are available at present. He is confident that, if money and interested workers are available, chemotherapeutic research will ultimately discover chemical agents capable of specifically destroying pneumococci and streptococci in the tissues as efficiently as arsphenamine and its congeners act in the destruction of Spirochaeta pallida. At the present time the dyes, such as gentian violet and acriflavine, and such chemical agents as optochin hydrochloride, iodine and mercurial compounds are but hopeful indications of what may follow the results of persistent and well organized chemotherapeutic research, which he believes constitutes one of the main hopes in the future of conquering dangerous bacterial infections. In streptococcus and pneumococcus meningitis and cerebral abscesses secondary to primary infections of the nasal accessory sinuses and mastoid cells, the problem of prompt and adequate surgical drainage still remains of paramount importance, as there are not available at present either immune serums or chemotherapeutic agents capable of disinfecting such areas by intracarotid or intravenous routes of administration. It is true that intracarotid injections are major procedures and that consequently one naturally hesitates to resort to them; but if there is any lesson that should have been learned by this time it is that methods of treatment of acute, diffuse purulent pneumococcus and streptococcus meningitis by ordinary intravenous and intraspinal medication are usually hopeless procedures. With intracarotid injections there is nothing to be lost and possibly something to be gained when combined with prompt and radical methods for surgical dainage.

EDITOR'S ABSTRACT.

BILATERAL BLEPHAROSPASM AND "SEE-SAW" BLEPHAROSPASM OF ENCEPHALITIC ORIGIN. BEAUVIEUX, DELMAS-MARSALET and DESPONS, Rev. d'oto-neuro-opht. **9**:568 (Oct.) 1931.

The secondary manifestations of epidemic encephalitis present a curious polymorphism, notably perturbations of posture and alterations of muscular tonus. Two cases of blepharospasm are reported. In the first, that of a man, aged 32, a typical attack of epidemic encephalitis had occurred seven years previously. Examination revealed a mild parkinsonian state: immobile facies, bradykinesis, muscular hypotonia and exaggeration of the elementary postural reflexes. A bilateral blepharospasm involved especially the orbicularis and also the frontalis. The spasm was provoked by energetic closure of the lids, by blinking produced by a bright light or by percussion of the internal angle of the eye. The automatic reflex, the intrinsic motility and the fundi of the eyes were normal. The wearing of dark glasses and the ingestion of scopolamine solution and calcium chloride diminished the frequency of the spasms.

The second case was that of a man, aged 65, in excellent health, and with no significant past history except for an intense transient diplopia ten years previously. For the preceding month he had complained of troubled vision and attacks of blepharospasm, alternating from one eye to the other in a see-sawing manner. Examination revealed no sign of parkinsonism. Voluntary and associated movements of the globes and intrinsic motility were normal, as were the eyegrounds. The spasm was provoked by a forward inclination of the head but not by a bright light. The normal automatic reflex movements were disturbed, and the spasms were diminished by a backward inclination of the head.

These two observations are examples of the multiple pathogenicity of encephalitic blepharospasm. In the first, the disturbance affected the orbicularis and frontalis in their reflex relations with intense visual impressions. In the second, the blepharospasm was associated with disturbance of the normal mechanism of reflex orientation of the eyes in relation to displacements of the head. It is probable that some abnormality in the otolithic apparatus is responsible for the difficulty.

DENNIS, Colorado Springs, Colo.

MANAGEMENT OF SKULL FRACTURES AND INTRACRANIAL INJURIES. HARRY E. MOCK, J. A. M. A. **97**:1430 (Nov. 14) 1931.

Mock calls attention to the fact that the annually increasing morbidity and mortality rate due to trauma, with skull fracture causing a high percentage of the deaths, makes this one of the great economic and medical problems of the present time. It is impossible to standardize treatment, as each individual case presents its own peculiar requirements. But it is possible to give a rational routine treatment which can be applied to 50 per cent of all skull fracture cases and then to classify the remaining cases into the following three groups: (1) Those in which rest treatment alone is sufficient (4 per cent); (2) those patients who must have, in addition to routine care, the special treatment of lumbar drainage (33 per cent), and (3) those cases having definite, recognized indications for cerebrocranial operations (13 per cent). The author attempts to clear up certain controversies by detailing those practices recognized by the majority of authors on this subject and proved of the greatest value in his hands in the management of skull fractures and cerebrocranial injuries. His article was written for those men away from medical centers who are just as frequently confronted with these cases and who are sometimes led astray in their treatment by certain teachers decrying lumbar drainage and by other teachers extremely adept in operative technic, advocating operative intervention in skull fractures, especially decompressions. He believes that if the average man will delay all roentgen examinations, undue physical examinations and operative procedures (with a rare exception) until the initial shock is over and then will classify his cases according to their signs and symptoms, he will develop for himself a common sense, rational line of treatment free from many of the controversial pitfalls commonly found in the management of skull fractures. Skull fractures should be treated at or near where they occur. Specialists, if desired, should be taken to the patient with the skull fracture rather than the patient to the specialist. Since, in the majority of communities, specialists in this condition do not exist and since the automobile has become a potential carrier of skull fractures to every hamlet, village and city in the land, it behooves all with experience in this matter to simplify and clarify the management of skull fractures to the end that the majority of physicians can properly cope with this grave emergency when and wherever confronted with it.

EDITOR'S ABSTRACT.

PSYCHIC DISTURBANCES IN SOMATIC DISEASES. E. D. WIERSMA, J. f. Psychol. u. Neurol. **42**:480 (June) 1931.

According to Wiersma, an organic increase in vital energy, which produces, for example, muscular hypertrophy, corresponds to a psychic increase in the concentration of attention (higher level of consciousness). In both cases, i. e., as a result of an increase of vital energy as well as of the level of consciousness, purposeful centrifugal functioning becomes augmented. Similarly, there exists an analogous relationship between diminished vitality of a tissue destined for some purposeful function and diminution in the concentration of attention, or a lower level of consciousness, for in both of these instances there occurs a lack of inhibition as well as of conductivity.

If one could assume that the development of carcinoma bears some relation to a diminution in the vitality of epithelial tissue, a structure destined to regulate purposeful and useful activity, one could also assume that the development of new growths in other tissues may depend on a similar diminution of vitality in these tissues. Wiersma believes that the proliferation of excessive granulation tissue, which occurs under various circumstances, may also be based on a similar phenomenon. If all this be true, the cause of primary cerebral tumors may have to be looked for in a diminution in the vitality of brain tissue. This naturally presupposes a knowledge of the manifestations of the vitality of all animal tissues and the ability to determine precisely the characteristics of a diminution of purposeful vital functioning of each tissue. If such knowledge were available one could

hope to recognize, on the basis of physiologic phenomena, the "pretumorous stage" of a new growth. As most cerebral tumors are gliomas, the causes and manifestations of the diminution of normal function of glial tissue will have to be taken into consideration and carefully investigated. Wiersma believes that just as a diminution of consciousness favors the uninhibited purposeless production of ideas, so a diminution of somatic vital energy releases lower physiologic functions and brings them to the surface.

KESCHNER, New York.

THE HISTOLOGIC STRUCTURE OF THE SPINAL ROOTS. G. ANTONINI, Riv. di pat. nerv. **37**:108 (Jan.) 1931.

The author has studied from a histologic standpoint the anatomic structure of spinal roots, with the special purpose of establishing whether unmyelinated fibers are present among the myelinated ones. The author's investigation has been inspired by the well known studies of Ken Kuré and Tetsuschiro, who studied the presence of myelinated fibers in peripheral nerves in order to establish a correlation between the various muscular groups and other sympathetic innervation.

The method used by Antonini is that of silver nitrate impregnation after previous fixation in ammonia alcohol according to Cajal's technic or previous fixation in diluted pyridine according to Lugaro's modification of the method. The author illustrates with photomicrographs the occurrence of considerable numbers of unmyelinated fibers in the posterior roots. The difference in the cross-section of an anterior root and that of a posterior root consists in the fact that in the latter the unmyelinated fibers, which are more deeply impregnated with silver nitrate, are scattered throughout the sections among the myelinated fibers and at times are collected in bundles of three, four or more fibers. The contrast between the unmyelinated fibers and the myelinated ones consists in the existence of a clear hollow representing the myelin covering in the myelinated fibers, whereas, the unmyelinated fibers are represented by more or less punctiform black dots not provided with a covering. In longitudinal sections the unmyelinated fibers, more numerous in the posterior roots, appear as deeply stained structures collected in bundles of five, six, seven or more individual fibers. The author has studied the spinal roots of dogs and of two human beings, and the results are comparable. The number of unmyelinated fibers in the posterior root is so considerable as to attract attention definitely to this system of fibers, which must take part in all the functions of muscular tonus, trophism and vasomotor regulation over which the posterior root presides.

FERRARO, New York.

INDISPENSABLE USES OF NARCOTICS: PSYCHOTHERAPY AS A SUBSTITUTE FOR NARCOTICS. R. B. RICHARDSON and T. H. WEISENBURG, J. A. M. A. **96**:1574 (May 9) 1931.

Throughout the years 1925 to 1929, Richardson and Weisenburg collaborated in the intimate study of 125 patients addicted to the use of "habit-forming drugs" and observed others to whom the same drugs were prescribed in the ordinary practice of medicine for the relief of pain and discomfort. This proved to their satisfaction that fewer narcotics would be administered for the alleviation of distress if those who practiced the healing art were more conversant with psychotherapy: that in psychotherapeutic principles there is a substitute for narcotics in many cases, and when there is no alternative but to use habit-forming drugs on account of severe and prolonged pain, the amount prescribed should be kept to a minimum. The data collected from all sources were most convincing that there is no physical basis for the justification of a narcotic addiction: that it is entirely a developmental and psychologic problem, the only approach to which lies through the application of psychotherapeutic principles. Psychotherapy in terms of drug addiction means giving the patient something to live for. It is not possible to lay down precise rules for rendering their difficulties innocuous since no two personalities are composed of the same combination. It is necessary to

study the mosaic of the patient's life to discover something that will blend with its coloring. It is a matter of transforming defeat into victory. This can be accomplished by fully understanding the patient's personality, environment, difficulties and outlook on life, and then with the infinite patience of a wise parent putting better things in his way. Fewer narcotics might be prescribed if those who treated human ills interpreted distress in terms of personality rather than in symptoms of the physical machine. It is not the intention to suggest or infer that narcotics might be banished from medical use: They still have their place; but he who prescribes such drugs on the least provocation is practicing medicine indolently.

EDITOR'S ABSTRACT.

PERMEABILITY OF THE HEMATO-ENCEPHALIC BARRIER IN PATIENTS WITH MENTAL DISEASE. C. E. ROBERTI, Rassegna di studi psichiat. **20**:663 (July-Aug.) 1931.

The importance of the study of the permeability of the hemato-encephalic barrier becomes apparent when the conclusions of Walter are recalled concerning the distinction made between schizophrenia and symptomatic psychoses due to toxic factors. According to Walter, in toxic encephalitis there is an increase of permeability, contrasting with a decrease as reported in schizophrenia. Following Walter's studies, Flatau has devised a new method of investigation of meningeal permeability, which is called the chromoneuroscopic test and consists in the intramuscular injection of Grübler's acid fuchsin, with the consequent passage into the cerebrospinal fluid of chromogen, which can be detected by the use of the following reagent: 9 cc. of 95 per cent alcohol and 1 cc. of hydrochloric acid, which in contact with chromogen will give a violet reaction.

Roberti studied ninety cases of various mental conditions at a stationary period or during manic excitement, during which, according to Monakow, the permeability of the barrier is more easily involved. The conclusions are that: (1) In patients with mental disease Grübler's acid fuchsin does not pass through the hemato-encephalic barrier. (2) The supposed meningeal involvement (chronic leptomeningitis of dementia paralytica, leptomeningitis in cases of severe amentia, chronic alcoholism, arteriosclerosis, etc.) does not seem to be sufficient to allow the passage of acid fuchsin into the cerebrospinal fluid. (3) The agitated periods of dementia praecox do not generate abnormal conditions of permeability of the meninges as detected by the Flatau test. (4) No difference in the behavior of the permeability of the barrier is found in dementia paralytica before or after malarial treatment. (5) The only positive test that one patient showed is related, according to the author's opinion, to the more general nutritional condition of rickets and ichthyosis that were present. (6) Age has no influence on the permeability.

FERRARO, New York.

RÔLE PLAYED BY THE CUTANEOUS SENSES IN SPATIAL PERCEPTIONS. WILLIAM MALAMUD and WALLACE NYGARD, J. Nerv. & Ment. Dis. **73**:465 (May) 1931.

The authors' experiments were carried on with thirteen college students regarded as normal controls and thirteen patients of the Psychopathic Hospital, eight having psychoneurosis, one psychopathic personality and four schizophrenia. The authors found that, in studies of space perception, normal persons show higher thresholds for two-point pain discrimination than for two-point touch discrimination. In the psychoneurotic patients the opposite result was found, namely, that the thresholds for pain are lower than those for touch. In the patient with psychopathic personality and in the four with schizophrenia, a similar reading resulted. The authors analyzed one of the neurotic patients suffering from a compulsion to kill her husband and son, and found a definite parallelism between the occurrences in the general behavior of the psychoneurotic person and the particular deviation in his perception of space. Thus the normal person tends

to distort certain space perceptions when the cutaneous senses are used without the control of the visual sense. In the psychoneurotic patient the authors found a tendency to overcompensate in favor of the environment, namely, by repressing the normal tendency to judge the painful stimuli as being nearer to one another than the tactile, and then to overshoot the mark by a reversal of the normal reaction. These perceptual characteristics are linked with the total behavior of the personality to indicate that they are not isolated phenomena, but closely interrelated aspects of the interaction of a special personality and its environment.

HART, Greenwich, Conn.

THE CAJAL-SMIRNOW FIBERS: A NORMAL COMPONENT OF THE HUMAN CEREBELLUM. K. VON SANTHA, Arch. f. Psychiat. **93**:142, 1931.

The Cajal-Smirnow fibers were first described by Cajal, who observed them in animals; subsequently they were demonstrated by Smirnow in dogs. Since then, attempts have been made to demonstrate these fibers in the human brain, but until recently they were thought to be present only in pathologic human material. The author has investigated the occurrence of these fibers in fifty human brains and in the brains of two monkeys, two dogs and two rabbits. The human brains were those of persons with schizophrenia, dementia paralytica, arteriosclerosis, senile dementia, and a number of other diseases. He comes to the following conclusions: These fibers are normal constituents of the human cerebellum. Their localization is restricted to the paleocerebellum, and they are most frequently found in the lobus anterior vermis and the flocculus. They come up from the white matter, traverse the cortex for a distance and return back into the white matter. They do not seem to originate in the Purkinje cells, nor do they have any definite relationship to the association elements of the cerebellum. They also seem to have no relationship to the afferent pontile fibers, so that they are apparently exclusively related to the elements that run into the paleocerebellum. The fibers show a tendency to proliferation in certain endogenous nervous diseases. (To the reviewer it appears somewhat unjustified to reach a conclusion as to the occurrence of these fibers in normal brains on the basis of a study of a number of brains that were exclusively those of patients with mental and nervous diseases.)

MALAMUD, Iowa City.

A CONTRIBUTION TO THE KNOWLEDGE OF THE MICROGLIA IN BIRDS. V. BELMONTE VENTO, Bol. r. Soc. españ. de hist. nat. **31**:349, 1931.

The author has studied the microglia in the chicken, sparrow and pigeon. The technic used was the method of del Rio Hortega. The staining capacity of the microglia varies according to the species. It stains readily in the chicken, but not so easily in the pigeon and sparrow. The descriptions given by the author refer chiefly to the microglia in the chicken.

In chicks, from eight to fifteen days after hatching, the microglia already appears with the characteristics of that found in the adult. Microgliocytes occur everywhere in the nervous system, in the white matter as well as in the gray matter, though they are more abundant in the latter, as is the case in mammals. The microgliocytes of the chicken are somewhat smaller than the mammalian, and the prolongations are correspondingly thinner. The nuclei are polymorphic. The distribution of the microgliocytes is similar to that of the corresponding element of mammals, but they are not so abundant in the cerebellum of the bird. In all other respects, the avian microglia is identical with the mammalian.

The author has also studied the microglia in experimental wounds produced with a heated needle. In the chicken and pigeon, the mobilization of the microgliocytes takes places from twenty-four to forty-eight hours after the wound has been inflicted, and the diverse aspects during their migration toward the affected area can be followed. As in the mammal, the microgliocytes lose their prolonga-

tions to become round, ameboid cells, which ingest débris, especially red blood corpuscles in diverse stages of their disintegration. Many microgliocytes appear under the form of rod cells, which are formed in early stages, while others are changed into the fat-granule cells so characteristic of mammalian lesions.

NONIDEZ, New York.

A CASE OF OPTIC ATROPHY WITHOUT PAPILLEDEMA IN A TUMOR OF THE FRONTAL LOBE COMPLICATED BY HYDROCEPHALUS. A. RIFAT, Ann. d'ocul. **168**:206 (March) 1931.

It is pointed out by Rifat that cerebral tumors developing away from the region of the chiasm, in certain cases, produce a clinical picture that simulates tumors of the hypophysis. The case observed by him was that of a woman, aged 35, who showed signs of markedly increased intracranial pressure and symptoms of involvement of the chiasm, notably, simple optic atrophy and alteration in the sella turcica. There was also complete loss of the sense of smell, mental involvement and facial paresis of the central type. The cerebrospinal fluid showed a marked increase in albumin with no increase in the cell count. The clinical picture indicated the presence of a tumor of the frontal lobe. The anosmia suggested localization in the anterior cranial fossa. The psychic symptoms were not marked, in spite of the fact that both frontal lobes were shown at autopsy to have been involved with marked destruction of the right lobe. Simple optic atrophy developed, as the autopsy demonstrated, because the chiasm was compressed by the distention of the third ventricle.

Rifat states that it is rare for papilledema to be present in such cases. He also states that changes in the sella turcica do not always point to a tumor in the region of the chiasm. Changes in the sella have been reported in tumors located elsewhere and also in chronic hydrocephalus. In certain cases of internal hydrocephalus, the roentgenogram demonstrates a pathologic process in the sella turcica, although no signs of involvement of the chiasm or optic tracts can be noted.

BERENS, New York.

CONVULSIVE MANIFESTATIONS IN HUNTINGTON'S CHOREA. J. NOTKIN, J. Nerv. & Ment. Dis. **74**:149 (Aug.) 1931.

The author reviews the literature and finds convulsive seizures in Huntington's chorea not particularly common. Some nineteen authors have reported instances since 1880. The case of a woman, aged 55, with a family history of alcoholism and mental disease, is discussed by the author. This woman, at the age of 49, became more seclusive and apathetic, and indulged in moderate alcoholism; unsteadiness on her feet developed. Dizziness, pains in the head and more marked disturbance of equilibrium followed. Three years prior to commitment, delusions of persecution developed; she became forgetful, and seemed mildly depressed and unstable emotionally. Progressive deterioration set in, with poor orientation, unstable dancelike gait and convulsive seizures of generalized character, with loss of consciousness and somnolence. Speech became indistinct. The study of the pathology of the brain in the literature shows no uniformity of findings. Lesions have been found in the corpus striatum, precentral gyrus, frontal lobe and occasionally in the other cerebral lobes. Many of the unconscious attacks recorded in the literature are not accompanied by motor phenomena. In ten instances the convulsive attack preceded the onset of the chorea, and in six it occurred at the same time. In some cases one finds a history of involuntary movements in various muscle groups under emotional stress long before frank choreic movements appeared. Convulsive manifestations in other members of the family are recorded frequently enough in the literature to be of great significance, and suggest some relationship between Huntington's chorea and the idiopathic group of convulsive states.

HART, Greenwich, Conn.

THE CENTRAL TEGMENTAL TRACT (THALAMO-OLIVARY TRACT). ALFRED ALEXANDER, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **33**:261, 1931.

The central tegmental tract represents a system that, although not uniform in size, is present throughout the entire mammalian series. It attains its greatest development in man, in whom it occupies the characteristic position of being well limited to the center of the tegmentum. In animals, the location of this tract is rather indefinite although, in almost all of them, it is most distinct in the oral portion of its course. Next to the apes, the system is best developed in Carnivora and next in Artriodactyla and Perissodactyla as well as in Rodentia. It is strikingly poorly developed in Chiroptera, while in the remaining animal orders it exists only in the form of a few fibers.

Although the author's investigations of this tract do not warrant positive conclusions as to its origin, nevertheless he finds sufficient evidence to lead him to believe that its site of origin is in the mesencephalon. His assumption is based on the fact that in no animal could he find any fibers of the tract oral to the nucleus oculomotorius. The site of origin he believes to be chiefly in the central gray matter at the level between the nuclei of the third and fourth cranial nerves; it is from this level that the fibers can be seen definitely to enter the tractus centralis tegmenti. The other nuclei situated at the margin of the central gray, such as the nucleus darkschewitschii, seem to have some relation with the tract, at least with part of its fibers. Its connection with the striatum through the mesencephalon makes it an important link in the striocerebellar mechanism, and as such it assumes the significance of a mesencephalo-olivary tract.

KESCHNER, New York.

TWO CASES OF SYPHILITIC SPONDYLITIS. CHRISTINE ABERNETHY, Brit. M. J. **1**:1112 (June 27) 1931.

Because of the rarity of syphilitic spondylitis reported in the literature, two cases are recorded. Both showed a history of rheumatism extending over ten years. The first patient was 36 years of age. Although he had complained of pain in the arms and shoulders, improving and relapsing, prior to being crushed between heavy gates, subsequently pain in the thoracic wall, shoulders and neck was attributed to the accident. A roentgenogram revealed a dislocation of the atlas forward on the axis, and that the first three cervical vertebrae were carious. Fixation gave only temporary relief. Two months later, a bony tumor developed in the lower third of the humerus, and was diagnosed by the roentgenologist as nontuberculous and suggestive of syphilis. The Wassermann reaction was positive. A British preparation of neoarsphenamine brought about uninterrupted recovery from the spinal condition, but a fracture occurred through the gumma in the humerus and failed to unite. The second case was in a man, aged 41, who eighteen months before admission to the hospital had had a series of abscesses over the sternum and in the region of the parietal bones. These had broken down and some had healed. Suspicions of syphilis were confirmed by a positive Wassermann reaction. Three weeks later, because of the complaint of pain and stiffness in the neck, roentgen examination was made, and early destruction of the third cervical vertebra was found. Rapid improvement followed the administration of neoarsphenamine and the application of a surgical support. Roentgenologically, the lesion was soundly healed at the end of nine months.

FERGUSON, Niagara Falls, N. Y.

THE RELATION OF ACHLORHYDRIA TO PERNICIOUS ANEMIA. ELI MOSCHOWITZ, Arch. Int. Med. **48**:171 (Aug.) 1931.

In view of the changes in the spinal cord so frequently associated with it, neurologists will be interested in Moschowitz' presentation of the position of achlorhydria in the pernicious anemia syndrome. That the achylia gastrica is a primary and not a secondary feature of the disease is evidenced by the constancy

of its appearance, by the fact that it precedes the blood changes and does not improve during a remission, and that there is no stage of diminishing gastric acidity even very early in the course of the pernicious anemia. Moschowitz is skeptical about the hypothesis that the Bothriocephalus latus is an etiologic agent, pointing out that in some parts of the world, as, for example, areas in Finland, infestation with this parasite occurs in 30 per cent of the people, while anemia is observed in less than 1 per cent. He speculates as to the relationship between achlorhydria and secondary anemia and considers it a reasonable, but unproved possibility. Among apparently normal persons achlorhydria has an incidence of about 0.2 per cent. He cites Crohn's report that 40 per cent of the apparently healthy children of parents with pernicious anemia show achlorhydria, and quotes Levine's finding of a 60 per cent familial incidence in this disease. He concludes with the observation that achlorhydria is the most tangible evidence of the constitutional background of pernicious anemia. DAVIDSON, Newark, N. J.

PAINFUL CONTRACTURES IN FLEXION OF THE LOWER EXTREMITIES FROM UNILATERAL CEREBRAL LESIONS. L. TCHLENOFF and C. CHAIMÉ, Encéphale **26**:438 (June) 1931.

In 1925, a report was given by Vincent, Krebs and Chavany of two cases in which a unilateral cerebral lesion was accompanied by flexion spasms of the lower extremities. The syndrome, as worked out then, consists of more or less marked obtunding of the intellect; severe hemiplegia; severe pain, generally localized in the lower limbs; hyperalgesia to contact; contracture of the lower limbs and reflexes of defense on the hemiplegic side. At autopsy these two cases showed: the one, an infarct of the external capsule, putamen and other cell masses of the lenticular area; the other, a unilateral cerebral lesion conditioning partial degeneration of the one pyramid.

The authors present a case almost identical in symptomatology. A woman, aged 48, manifested a progressive development along the lines given, and at autopsy showed extensive softening of the sylvian area. The authors are thus led to conclude that the clinical picture can be produced by a lesion of the sensory area of the cortex, of the thalamus or of the tracts uniting the thalamus and the parietal lobe. They consider the syndrome as a definite unit, based on the liberation of thalamic and thalamopallidal functions from cortical and neostriatal inhibition. ANDERSON, Los Angeles.

A CASE OF PERNICIOUS ANAEMIA RESISTANT TO TREATMENT. A. M. KENNEDY, Brit. M. J. **2**:5 (July 4) 1931.

A man, aged 52, noticed that he was becoming pale and tired easily. A year later, he sought treatment in a convalescent home for a year. The symptoms increased, and six months later he was told that he was suffering from pernicious anemia and was given from ¼ to ½ pound (120 to 240 cc.) of liver daily. After six months of treatment, his condition was unchanged, and he was admitted to the hospital under the author's care. The course in the hospital extended from April 25, 1930, to March 21, 1931, when he died of bronchopneumonia. He was treated first with liver, later with desiccated extract of stomach tissue and then with multiple vitamins (A, B, C, D and E), during which improvement took place for two and a half months, but was not maintained, and a relapse ensued. Liver extract and desiccated extract of stomach tissue were then given, with several transfusions of blood, but the relapse progressed and ended in death. The author remarks that the improvement under administration of the vitamins may have indicated nothing more than a natural remission. Autopsy confirmed the diagnosis of pernicious anemia. An unusual feature of the case was the presence of hydrochloric acid in the stomach contents. Otherwise, the clinical picture was typical of addisonian pernicious anemia. FERGUSON, Niagara Falls, N. Y.

EPILEPTIFORM SEIZURES OF JACKSONIAN CHARACTER: ANALYSIS OF ONE HUNDRED AND THIRTY CASES. E. F. FINCHER, JR., and CHARLES E. DOWMAN, J. A. M. A. **97**:1375 (Nov. 7) 1931.

One hundred and thirty cases presenting localized convulsive attacks either motor or sensory in character are analyzed. In regard to the underlying etiologic factors, the cases fall into the following groups: (1) brain tumor, 24.6 per cent; (2) trauma occurring after birth, 20 per cent; (3) birth trauma, 14.6 per cent; (4) postinfection, 10.7 per cent; (5) cerebral atrophy of undetermined cause, 5.2 per cent; (6) syphilis, 5.3 per cent; (7) palsies of childhood of undetermined etiology, 3.8 per cent; (8) arteriosclerosis, 3 per cent; (9) miscellaneous causes, 3.8 per cent; (10) undetermined etiology, 8.4 per cent. There were ninety-one males and thirty-nine females in the group. In sixty-nine of the cases exploratory craniotomy was advised, and in sixty-two it was performed. The treatment in the cases in which operation was performed consisted, in general, of the removal of tumors, the excision of a cortical cicatrix, and the destruction of the so-called epileptic zone if no gross lesion was demonstrated. The results in the cases in which operation was performed seem to support the opinion that exploratory craniotomy is a justifiable procedure in all cases presenting localized epileptiform seizures in which the possibility of uncovering a removable lesion or destroying a demonstrable epileptic zone exists.

EDITOR'S ABSTRACT.

PSYCHOANALYSIS AND MEDICINE. FRANZ ALEXANDER, J. A. M. A. **96**:1351 (April 25) 1931.

The author sees the significance of psychoanalysis in its relation to medicine in the following two accomplishments: 1. With the help of a technic specifically adapted to the nature of psychic phenomena it developed a consistent and empirically founded theory of the personality suitable to serve as a basis for the understanding and treatment of mental disturbances. 2. It gave a concrete content to the philosophic postulate which considers living beings as psychobiologic entities by investigating in detail the interrelation of physiologic and psychologic processes. The greater part of these investigations must, however, be left to the future to be accomplished. He confesses that he feels his presentation incomplete because he touched only the actual results of psychoanalytic investigation and focused his interest on the method. But he thinks that it is more interesting and important for physicians to hear about the scientific nature and methodology of psychoanalysis if they desire to become oriented toward this young science so widely challenged, so problematic, and still so unknown. If the reader has obtained the impression that the method itself is sound, it is of secondary importance whether the results are finally tested or not. If the method is sound, in time the results must also become sound and acceptable.

EDITOR'S ABSTRACT.

OBESITY, CONSTITUTIONAL OR ENDOCRINE. SOLOMON SILVER and JULIUS BAUER, Am. J. M. Sc. **181**:769 (June) 1931.

The present concepts of the nature of obesity are critically reviewed, and the dangers of an "endocrine diagnosis" are mentioned. Obesity must be considered as a failure of the mechanism that normally keeps the weight of adults constant, thus stressing its endogenous nature. In Bauer's 400 cases, occupation played an insignificant rôle. The two main factors, the appetite and the energy expenditure, may be ill balanced. Perversions of appetite occur in organic and functional disease of the central nervous system, viz., "cerebral obesity"; increased appetite (hyperinsulinemia with hypoglycemia) and depression of the oxidative changes (hypophyseal cachexia and Addison's disease) are not always accompanied by an increase in weight. The constitutional concept of obesity considers this exag-

gerated tendency of some tissues to store fat (lipophilia), and possibly water and salts, as the primary factor in the causation of the obese state. The perversion of metabolism is explained as the result of a congenital factor already present in the fertilized ovum. Bauer could demonstrate the familial incidence of obesity in some 88 per cent of his cases, and found that only 2.6 per cent of 275 cases of obesity had their origin in disturbances of the glands of internal secretion.

MICHAELS, Detroit.

MENTAL HYGIENE IN TEACHER-TRAINING INSTITUTIONS IN THE UNITED STATES. CHARLES E. BENSON and LOUISE E. ALTENEDER, Ment. Hyg. **15**:227 (April) 1931.

From 239 normal schools, teachers' colleges and private institutions for training teachers, Benson and Alteneder received information concerning courses in mental hygiene. A regular course in this subject is given in only 20 per cent of the schools; in most of these the course is elective, open for the most part to senior or graduate students. Four fifths of the institutions hold lectures on mental hygiene in connection with other courses, however. A psychiatrist is available for consultation, instruction and help in only 5 per cent of the schools.

The private teacher-training institutions seem more interested in courses in mental hygiene than the municipal and state schools. In 1920, a survey similar to this study by Benson and Alteneder was conducted by Burnham, and a comparison of the two reports shows significant progress in the last ten years. Programs have been enlarged, special courses have been introduced, and the technic of mental testing has been more widely studied. Perhaps the most important change has been the shift of emphasis from the abnormal to the normal, the change in objective from readjustment to prevention.

DAVIDSON, Newark, N. J.

REMISSIONS AND RELAPSES ASSOCIATED WITH PREGNANCY IN MYASTHENIA GRAVIS. L. P. E. LAURENT, Lancet **1**:753 (April 4) 1931.

The influence of pregnancy and sometimes of the menstrual cycle on the course of myasthenia gravis leads the author to the view that this condition is largely, if not entirely, brought about by endocrine disturbances. A case of myasthenia gravis is described in a woman, aged 49, who had been under observation for twenty-six years. There were many remissions, none, in this case, however, having any definite reference to the menstrual cycle. There was a striking relationship to pregnancy, however, although an attack did precede marriage. During six subsequent pregnancies a relapse occurred, each clearing after either a miscarriage or an artificial abortion. Two healthy children were born, both with marked ease and rapidity of labor. Percipitate labor has previously been reported in this illness.

BECK, Buffalo.

THE LOCALIZING SIGNIFICANCE OF IMPAIRED RESPIRATORY MOVEMENTS IN LESIONS OF THE SPINAL CORD. WALTER O. KLINGMAN, Bull. Neurol. Inst., New York **1**:136, 1931.

The author calls attention to the clinical significance of impaired respiratory movements as valuable means of detecting and localizing lesions of the upper part of the spinal cord; the innervation of the various groups of muscles concerned in respiration and the clinical evidence of impaired or lost function of these various groups are clearly given, as well as the levels of the segments that innervate groups of muscles. Clinically, variations in movements of the thorax are classed in five groups corresponding to various levels of the cord. Among the clinical conditions in which thoracic signs may be produced are poliomyelitis, syringobulbia, infectious myelitis, transverse lesion of the cord and tumors.

KUBITSCHEK, St. Louis.

PROGNOSTIC IMPORT OF A NEGATIVE SPINAL FLUID IN EARLY AND IN LATENT SYPHILIS. H. HANFORD HOPKINS, Arch. Dermat. & Syph. **24**:404 (Sept.) 1931.

That syphilis, when it invades the nervous system at all, does so during the first few months of the infection is the thesis of Hopkins. He cites in evidence, a follow-up study of over four hundred syphilitic patients, all of whom had normal spinal fluids during the first year, and only 3 per cent of whom subsequently developed cerebrospinal syphilis. The few cases that did develop were mild, and not a single one of the patients suffered from either tabes or dementia paralytica. Hopkins concludes that, in a vast majority of cases, a normal spinal fluid during the first year of syphilitic infection warrants the presumption that syphilis of the central nervous system will not develop. DAVIDSON, Newark, N. J.

MULTIPLE CEREBRAL SPINAL ANGIOSPASMS SIMULATING MULTIPLE SCLEROSIS. F. BREMER, J. de neurol. et de psychiat. **31**:493 (Aug.) 1931.

The author states that angiospasms of the central nervous system may establish a syndrome that is similar to multiple sclerosis. The symptoms of such an involvement are extremely variable, and in certain cases may be allied to Raynaud's disease. The symptoms are inconstant and extremely variable as to location, involving even the medulla. Bremer states that during the past few years he has had an opportunity to observe several cases of this sort, which have been associated with symptoms of diplopia, paresthesias, paraplegia, scintillating scotoma, transient hemianopia, syncope, etc. Organic sequelae often persist. Treatment in these cases by sedative and continuous antispasmodic medication has given satisfactory results. WAGGONER, Ann Arbor, Mich.

THE EFFECT OF LECITHIN ON THE CEREBRAL CORTEX. ALEXANDER LINDBERG, J. f. Psychol. u. Neurol. **42**:465 (June) 1931.

Lindberg studied the effects of the continuous subcutaneous administration of lecithin on the cortical activity in dogs by employing Pavlov's method of conditioned reflexes. The effects of single subcutaneous injections of this substance on the central nervous system had previously been studied by other observers who found marked increase in the excitability and functioning of various parts of the nervous system. In Lindberg's experiments the lecithin did not produce an increase in excitability but an "augmentation of power of the central nervous system"—an increase in the power of resistance during the period of transition between "diminished excitability" and normal activity. KESCHNER, New York.

DISTURBANCES IN HANDWRITING AND CLUMSINESS AS SIGNS OF TOXIC GOITER. HENRY J. VANDEN BERG, Am. J. M. Sc. **182**:114 (July) 1931.

In the author's experience, patients with toxic goiter may be troubled with tremulous handwriting. The handwriting in five such cases before and after surgical treatment illustrates his contentions. As tremor is one of the cardinal symptoms and signs of exophthalmic goiter, the author asks, why should it not affect one's handwriting? Disturbances in handwriting and "clumsiness" may be hints of an early or mild case of exophthalmic goiter. MICHAELS, Detroit.

SEPTICAEMIA AND ENCEPHALITIS IN RELATION TO VACCINATION. ROBERT PRIEST, Brit. M. J. **1**:349 (Feb. 28) 1931.

The clinical and postmortem observations in the case of a patient who died twenty-three days after vaccination are reported; the symptoms suggested encephalitis, yet at the same time there were evidences of septicemia. Autopsy proved

conclusively that the symptoms and death were due to the latter. The author emphasizes the importance of a differential diagnosis between these two conditions in all patients who become ill following vaccination.

FERGUSON, Niagara Falls, N. Y.

COMPARISON OF THE CAPACITY OF ANTERIOR-HYPOPHYSEAL TISSUE OF MATURE AND IMMATURE FEMALE RABBITS TO INDUCE OVULATION. J. M. WOLFE and RUCKER, Anat. Rec. **51**:213, 1931.

Seventy-one rabbits were injected with hypophyseal tissue. Anterior-lobe tissues taken from immature female rabbits, as young as 3 months of age, and from mature females have equal capacity to induce ovulation. Anterior-lobe tissue from very young female rabbits (4 weeks) was deficient in the factor that causes ovulation.

COBB, Boston.

THE MECHANISM OF VASODILATATION FOLLOWING THE STIMULATION OF ANTIDROMIC NERVES. A. W. KIBJAKOW, Arch. f. d. ges. Physiol. **228**:30, 1931.

Following stimulation of the posterior roots of cats and rabbits, the blood of the corresponding limb acquires vasodilator qualities. The same is true for a Ringer solution which is perfused through the vessels of a limb, the posterior roots of which are stimulated. These experiments support the theory of Langley that the antidromic impulses conducted in sensory nerves produce chemical substances in the periphery.

SPIEGEL, Philadelphia.

Society Transactions

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

Joint Meeting, Nov. 10, 1931

S. PHILIP GOODHART, M.D., *President, in the Chair*

AVULSION OF BOTH EYES AND OPTIC NERVES BY A PATIENT WITH A POST-ENCEPHALITIC CONDITION. DR. S. PHILIP GOODHART.

R. V., aged 16, was the youngest of eight siblings, with a good family history, whose developmental life contained nothing abnormal. The medical history showed no sequelae from the usual diseases of childhood. Psychosexual development was without unusual features. The source of the present physical and mental state was an attack of encephalitis at the age of 8. The outstanding symptoms of the acute phase of the disease were a mild febrile period characterized by somnolence, although during the greater part of this period she was ambulatory. A few months later, character and personality changes were noted — undue irritability and anger in reaction to ordinary situations, and sudden tantrums, such as striking at the window, tearing clothes and smashing things about the house. Within a few months, left-sided extrapyramidal symptoms appeared (hemiplegia). She was observed and treated at Mount Sinai Hospital (1925) and at the New York Neurological Institute (1928). When 14, she first began to show a tendency to the self-infliction of injury; she would lock herself in a room and beat her body. In 1930, she started the removal of her own teeth. She was admitted to Morrisania Hospital in July, 1931, with mild ophthalmia of both eyes, probably due to irritation by her own manipulations. At Morrisania Hospital she avulsed both eyes with the optic nerves attached. There was little bleeding at the time. She stated that her eyes "just popped out." Physical examination at the Morrisania Hospital after avulsion revealed normal sensory responses throughout; in fact, she was very sensitive to painful stimuli. On the motor side, a left extrapyramidal type of hemiplegia was present. The patient was later removed to Montefiore Hospital. Psychiatric examination revealed little; the patient was well oriented; the stream of thought was normal, with no gross evidence of intellectual enfeeblement; the affective responses were adequate. She became depressed and tearful when the subject of self-mutilation was discussed. She finally admitted removal of the eyes, saying: "Something made me do it." She was edentulous.

ACUTE INTRACRANIAL EDEMA COMPLICATING OTITIS MEDIA. DR. FOSTER KENNEDY.

For some time it has been realized that localized intracranial edema can produce important neurologic signs. One is aware of it when angioneurotic edema occurs in other parts of the body, and appearing in the brain, produces transient cerebral symptoms. One is also aware of it as a sequel of serum administration and as a manifestation of serum sickness. About two and a half years ago, I was asked one morning to see a child, aged 10, who had had what appeared to be a serious cerebral accident an hour before. The child was in the Hospital of the Rockefeller Institute for nephritis, having in addition chronic left otitis media. The child had had no previous cerebral symptoms whatever. At 9:30 a. m. the nurse approached the child to feed it (having washed it earlier and found it intact and as usual) but it could not talk or raise the right arm. The nurse notified the doctor who at about 10 called me. I saw the child at 10:30, and found complete hemianopia, severe aphasia and total right hemiplegia with much

right hemianesthesia. The optic nerves were normal. The child was very drowsy. The history of the onset was so sudden and yet so subacute that the theory was made that the child was suffering, not from an intracranial vascular accident, but from an edema, the joint result of nephritis and a septic focus with local irritation of the meninges and brain. It was rather a rash diagnosis, as I was not familiar with that kind of edema, though interested in intracranial edema in general. I was delighted and amazed to find that the child at 5 p. m. that day had no hemiplegia, no hemianopia and no aphasia. The child was talking normally, and the Babinski sign had vanished. This is an example, the only very good example I have ever seen, of localized cerebral edema complicating otitis media.

Another case is more in line with those reported lately by Symonds in *Brain*. The child is now well. She is 12 years old. Three years before, she had double otitis media and a left mastoidectomy was performed. In April, 1931, she awoke with pain in both ears and a temperature that reached 105 F. Ten days later, she had double vision. A right mastoidectomy was performed, and chronic mastoiditis was found. In the two events, three years before and early in May, she had a double mastoidectomy. After the last operation she had a febrile temperature between 104 and 107, with, however, almost no headache. In that way she differed from Symonds' patients, in all of whom there was severe headache. She had a marked discharge from the ear for a week, which then stopped. She was perfectly well mentally, being alert and bright throughout. Some nausea, but no dizziness, was noted. Blood cultures gave negative results. No stiffness of the neck occurred. Except for strabismus and diplopia, vision was very good. There was marked bilateral papilledema, discovered, I believe, by accident in the course of routine examination. In the course of the mastoid operation, the lateral sinus was exposed and found to be uninfected. A spinal tap was done; the fluid was under greatly increased pressure. The cell content was normal. Throughout the illness the patient was clear mentally, in that way differing from patients with brain abscess following otitis media capable of producing severe papilledema. She was merry, gay and never stuporous. There was a distinct weakness of the left sixth and a doubtful weakness of the left seventh nerve, but no involvement of the other cranial nerves, no hemianopia and no other cerebral signs. In spite of the fact that she had papilledema and palsy of the sixth and possibly of the seventh nerves, we were prevented from making a diagnosis of abscess because of her alertness. Dr. Brock said that he believed she had otitic hydrocephalus. I am not sure, however, that Symonds is altogether right in saying that these cases are the result of overproduction of ventricular fluid, and that they are cases of internal hydrocephalus. I am not sure that his cases are not more like my first case of definitely localized cerebral edema. Such conditions may easily be mistaken for abscess, and these considerations oblige one to have alternate diagnosis in mind. The child had a fever with papilledema for six weeks. Gradually they diminished and ended. She has now been well since last July, and I believe that she has no abscess, not even a latent one.

DISCUSSION

DR. J. H. LEINER: I wish to inquire of Dr. Kennedy as to the examination of the patient's visual fields. Did the case show a pure papilledema with resolution, or, in view of the toxic factor, was there any scotomatous involvement?

DR. KENNEDY: A note of mine on June 3 says: "Since an abscess acting like a tumor might impinge on Meynert's bundle it would be wise to map the visual field carefully. A discovery of a hemianopic effect would support the diagnosis of a right temporosphenoidal abscess." However, there was no such evidence.

DR. J. RAMSAY HUNT: Was there any increase in vascular tension in the first case, that of nephritis?

DR. KENNEDY: I am sorry that I do not know.

DR. SAMUEL BROCK: If one wants to differentiate cerebral abscess from cases of this so-called hypertensive meningitis (Aboulker), one may say that the evolution of symptoms in this syndrome is much faster; that the headache is usually

more severe than in cerebral abscess (although in this case there was little or no headache); that the papilledema is much more intense in this syndrome, and that the temperature range is much higher in this type of case. Furthermore, the general condition of the patient is good, the mentality being alert. The cerebrospinal fluid pressure in these cases is very high, with no other abnormal findings in the spinal fluid. Strangely enough, there is very little evidence of any meningeal irritation, such as cervical rigidity, etc. It might be mentioned that the treatment for this condition is repeated spinal puncture. Occasionally, ventricular puncture is necessary. With such therapy the patients recover, just as did Dr. Kennedy's patient. The points cited are well covered by Symonds (Otitic Hydrocephalus, *Brain* **54**:55, 1931).

THE ACTION OF BULBOCAPNINE IN ANIMALS WITH VARIOUS EXPERIMENTAL LESIONS OF THE NERVOUS SYSTEM. DR. A. FERRARO and DR. S. E. BARRERA.

When injected into animals, bulbocapnine, an alkaloid obtained from Corydalis cava, has been found to produce a condition of catalepsy. This is characterized by two main elements, a loss of motor initiative and a preservation of passively impressed attitudes. Besides these, other phenomena can be observed in animals, as, for instance, the occurrence of negativism, hyperkinesias, vegetative disturbances, etc., depending to a great extent on the dosage. The effects of the drug on various animals (from those low in the scale without a neocortex to mammals having a better developed pallium) have led two of the main investigators, de Jong and Baruk, to these two important conclusions: 1. When it is injected into animals, especially mammals, bulbocapnine produces a clinical picture identical with catatonia in man. 2. The presence of the neocortex is essential for the occurrence of this experimental catatonia. Likewise, Schaltenbrand concluded that the motor cortex is essential for the production of catalepsy from a study of the effects of bulbocapnine in the acute state of cats operated on.

In order to substantiate the conclusions of de Jong and Baruk, and to extend observations to monkeys in both the acute and chronic stages and to cats in the chronic stages, we performed a large series of experiments in cats and monkeys, including the injection of bulbocapnine into normal animals and the injection of the same drug in similar doses into animals with various experimental lesions, as follows: removal of one motor area; removal of both motor areas; removal of the occipital area; removal of one or both cortical hemispheres; lesion of one or both sets of basal ganglia; removal of one and both hemispheres down to the thalamus; mesencephalopontile lesions; removal of the cerebellum; hemisection of the cervical cord; unilateral section of dorsal and ventral roots; bilateral superior cervical ganglionectomy combined with bilateral stellate and bilateral lumbosacral sympathectomy.

As a result of this investigation we conclude that cataleptic manifestations occur, not only in normal animals, but also in animals following the removal of the entire cortex and the basal ganglia on both sides, proving, therefore, that the presence of the cortex is not essential to the production of bulbocapnine catalepsy. The cataleptic manifestations in decorticated and thalamic animals occur not only in the so-called chronic stages, but also in the acute stages following operation. This differs from the reports of Schaltenbrand and Krause, who maintain that in the acute stage of the experiment catalepsy is not reproducible. We also contest de Jong and Baruk's conclusions that experimental catalepsy in animals is identical with human catatonia, because of the very important fact that only one component of catatonia may be experimentally reproduced, that is, the motor component. We speak of the psychomotor component of catalepsy, as Baruk and de Jong do, because of the appearance of catalepsy in the absence of the cortex.

However, the fact remains that a very important conclusion is reached from the psychiatric standpoint. This consists in the experimental reproduction of

catalepsy by means of toxic agents. The fact that these toxic manifestations may be experimentally reproduced in the absence of the cortex is an argument in favor of the toxic origin of at least some of the manifestations of mental disease which often have been considered as psychogenic in nature. Our investigation constitutes a stimulus for further studies in the organic approach to mental diseases.

DISCUSSION

DR. H. A. RILEY: It was interesting to me that bulbocapnine disturbances had been sublimated into the actual psychic sphere. I had always considered the bulbocapnine phenomenon as more or less a purely motor manifestation, and when it is definitely compared to the situation in catatonia and catalepsy in a supposedly psychotic person, it implies a much more extensive connotation than it does on the more simple basis. The picture of the monkey under the influence of bulbocapnine did not appear to me like the picture seen in catatonia, although I have not had a very extensive experience with catatonic patients. As the monkey faced the camera, the eyes were actively moving; the lids were closing, and there was an actual look of intelligence in the animal's eyes, which seems to me to be rather foreign to the reaction of the psychotic patient in catatonia or catalepsy. I should feel very much better satisfied if I had seen some of the pictures of these animals after the operation, but before the administration of bulbocapnine. Dr. Ferraro did not say very much about the contrast in activity following these extensive operations, that is, the basic activity of the animal, and that later modified by the injection of bulbocapnine. This is the main question that is raised in my mind: How different was the activity of these thalamicstriatal animals before and after bulbocapnine? It is difficult to reconcile the very divergent results of two competent observers, such as Drs. Ferraro and de Jong, and I imagine that only frequent repetition of this sort of investigation will result in a definite understanding of the situation.

DR. L. S. ARONSON: I wish to ask Dr. Ferraro what his experiences were with these bulbocapninized animals. There are at least three points that were not brought out in his paper, which he may have omitted purposely. One is whether bulbocapnine is a drug affecting only the motor system. I noticed that one of the cats had a very definite sensory disturbance, in that the response to needle prick was quite quick, whereas the response to deep pressure on the tendons was practically nil. While I observed all these rigidities with lack of change in posture, there was a noticeable psychic element in these cats—a snapping, growling, fighting attitude when you approached them. Handicapped as they were by their muscular rigidity, they presented a certain amount of combativeness. Though they hung on a chair, or two chairs that were gradually separated to the maximum, nevertheless, on approaching the cat, a hissing, snapping or spitting response was elicited. Lastly, I wish to know whether there was not occasionally another element, that is, a selective action on the optic nerve. Two of these cats, one a small kitten, were evidently blinded, because they walked right up to a box and would stay there with their eyes wide open and not move away from the object for an hour or even longer. They were not disturbed by the flashlight. I had no means of knowing whether ophthalmoscopic examination revealed anything in comparison with the other cats. I wish to ask whether bulbocapnine affects other parts of the nervous system, or especially the optic nerve and the sensory pathways?

DR. S. E. JELLIFFE: Regarding the pharmacology of bulbocapnine, it is supposed to be very closely related to an isomer of apomorphine. Corydalis belongs to the poppy family and bulbocapnine to the morphine group. So we are dealing with a drug that poisons the entire body. It is not limited to any one type of structure. It is unnecessary, though it is interesting, of course, to learn that catalepsy is not a situation due to cortical loss. Yet insects show primitive cataleptic motor attitudes and they have no cortex. Birds, rabbits, frogs, turtles, hens and other lower forms all show similar phenomena, and we know that in

them the neocortex amounts to little. In other words, these poisoned animals have been reduced to spinal or even peripheral muscle animals. They have been reduced to the last extreme of hypervigilance, using Head's illuminating conception. They are like some of Mr. Bellows' engravings of boxers, fighters, etc., just waiting, vigilant as they can be, hanging onto their last remaining breath that there may be some preservation of their life. We do not have to be told how frequently catalepsy is used as a defense mechanism. We know how many lower animals show similar phenomena in the presence of dangerous enemies. The unconscious wisdom of the entire body — instinctive defense if you will — shows itself, as when a predatory animal comes near a nesting duck, for instance.

Then I was very much interested in another remark, which I previously put in a more or less syllogistic form. As I recall the syllogism, it runs like this: Bulbocapnine will produce catatonia. Bulbocapnine is a poison. Ergo, catatonia is due to a poison. It strikes me that that is fundamentally false logic, whether one is dealing with bulbocapnine, choline, morphine, mescaline or any other poison. I need not go into a long disquisition on the differences between catatonia in the human being as a disease concept (Hecker to Bleuler) and that in animals. It strikes me that the logic of the situation as just expressed is totally upset by a simple experiment. Many of you have seen it tried, and many of you have seen moving pictures of it. Give a profoundly catatonic patient another poison, sodium amytal, for instance, and he will be rendered perfectly normal for the time being. Claude did it first with ether. In other words, a symptom produced by a poison is cured by another poison. Catatonia in man is a hypervigilant situation. It is largely a defense mechanism in which the person is operating on the positive side (Hughlings Jackson) in response to uninhibited incoming stimuli. The poison does not per se produce the motor attitude; it prevents its inhibition or repression, and elemental motor attitudes appear. What the negative side may be, I am not prepared to say, but it seems to me that the problem will never be solved along this so-called experimental organic side, no matter how interesting and important it may be from other angles. Of course, everybody knows that to have any activity of the human body an organ must be used, and that the absolute distinction between organic and functional is a left-over of the scholastic separation of body and soul nonsense begun by Plato. Even "Casey" knows that you need a bat to hit the ball, and so in order to have any symptom organs are needed. The approach from the negative side is of interest, and it is of great significance and importance; I thoroughly agree with Dr. Ferraro that de Jong's and Baruk's investigations are filled with errors, not of observation or of description, but of interpretation. From 1921 onward, I have been fortunate in seeing de Jong's animals since he began his experiments, and I have followed his most valuable experiments with great interest and sympathy; however, I am convinced that these investigators have not considered the Jackson conceptions from their interpretative side. Surely, hypnosis can bring about a cataleptic or a catatonic motor attitude, and certainly hypnosis does not operate through "poisoning."

DR. JOSHUA ROSETT: The moving pictures of Dr. Ferraro's experiments show a remarkably complete catatonic and cataleptic state produced in monkeys by bulbocapnine. Yet one can hardly help being puzzled by his conclusion that the cerebral cortex and the corpus striatum are not necessary to the production of catalepsy and catatonia in animals. Thus stated, the matter appears to me to have been put far too mildly, for the following reasons: The three outstanding features of the decerebrate state are catalepsy, catatonia and plastic features. With reference to the cataleptic state of animals deprived of the cerebrum, Sherrington pictures them as appearing to be mildly asleep. The muscular rigidity is peculiar in that postures imposed on the animal tend to be maintained; that is to say, when a joint, for example, is passively flexed, the flexion is maintained for a much longer period of time than in a normal animal. The hundreds, perhaps thousands, of experiments reported by a large number of investigators agree on these three salient features of the decerebrate state. The effect of the administration of bulbocapnine

is to poison the cerebrum and thus to produce a result that is practically equivalent to removing the animal's cerebrum. Dr. Ferraro's experiments with the drug in question clearly demonstrate the latter fact. His conclusion, therefore, that the cortex and the striatum are not necessary to the production of catalepsy, catatonia and plastic tonus, is practically equivalent to a statement that the cerebrum is not necessary to the production of the decerebrate state, a statement which, to say the least, is rather puzzling.

DR. J. R. HUNT: The papers of the evening in the field of experimental neurology present several fundamental problems for discussion, among them the question of the dual nature of the efferent nervous system, a conception that I formulated over a decade ago (The Static and Kinetic Systems of Motility, ARCH. NEUROL. & PSYCHIAT. **4**:353 [Oct.] 1920).

According to this view, the whole efferent system is dual in nature. One component is kinetic and related to movement; the other is static and related to postural tone and posture — both working together harmoniously in the interest of motility. In this respect the efferent system resembles the afferent, which is composed of more than one component subserving the different modalities of sensation. The kinetic system is represented by the corticospinal (pyramidal tracts) and striospinal systems (extrapyramidal tracts), and the static system by the corticocerebellar and cerebellospinal systems. The chief ganglionic structure of the static system is the cerebellum; hence the importance of these experimental studies to the dual theory.

The neuromuscular representations of the efferent system are still under investigation; the kinetic system is represented by the somatic innervation of the striated muscle fiber (sarcostyles), and there is some evidence that the static system is represented by the sympathetic innervation of the striated muscle fiber (sarcoplasm). I think that the investigations with bulbocapnine intoxication touch on this question of neuromuscular innervation very closely. I agree with the other speakers that the evidence is much more in favor of this phenomenon being a muscular or neuromuscular manifestation than one of the central nervous system and this view finds support in Dr. Ferraro's experiments. It is possible that this drug may have an influence on the sarcoplasm and its sympathetic innervation be analogous to the effect of strychnine on the somatic component.

DR. J. H. LEINER: Following the work of Schaltenbrand and de Jong, and later a personal conversation with Schaltenbrand, Dr. Kaufman and I began an investigation in the use of bulbocapnine as a therapeutic measure in all nervous diseases manifesting states of hyperkinesis, i. e., parkinsonism either of the arteriosclerotic type or the inflammatory (epidemic encephalitic) variety, dystonia musculorum deformans, degenerative choreas (Huntington), multiple sclerosis, etc. The graphic part of this work has been published in the ARCHIVES; the cinematographic part will follow shortly.

Last summer, I spent an interesting day in the laboratory of Dr. Ferarro to view his material and correlate if possible the phenomena in his animals with those arising in the human being following the administration of bulbocapnine. I will say that both the cataleptic and catatonic states in the animal can be duplicated in the human being if sufficient bulbocapnine is administered, particularly in the parkinsonism of epidemic encephalitis. The study and control of tremors interest me, particularly the discussion and known views of Dr. Hunt relative to cerebellar tremors. Today a cinematographic study was made in a case of parkinsonism of the inflammatory type. The patient showed a mixed tremor of an apparent striatal variety involving the lower jaw and an intention tremor of cerebellar origin. The typical coarsely rhythmic tremor and one of constant amplitude was easily controlled by bulbocapnine, with catatonic-like facial display. The cerebellar tremor was more difficult to control, if at all, by therapeutic doses. I expect to show these cinematographic studies shortly. Dr. Ferraro showed that the action of bulbocapnine can exist despite the removal of most of the cerebral structures,

or as Dr. Rosett stated, it can persist after decerebration as well, which also leads me to think that the drug may possibly act on the sarcoplastic portion of the crossed striated muscle fiber through the nonmedullated system of paleostriatal origin.

DR. FERRARO: In reply to Dr. Riley, unfortunately the time allowed made it impossible to show animals after the various operative procedures but before the administration of bulbocapnine. We can assure him, however, that there was a striking contrast in the behavior of the animal before and after the administration of bulbocapnine, and that the animals, especially the ones with chronic disease, were extremely active and lively, most of them having compensated for their neurologic defect.

In reply to Dr. Aronson, we have observed all the psychic manifestations in cats, the fighting, spitting, hissing types of reaction, but these occurred with higher doses than those used to produce pure cataleptic manifestations. We have also found the disturbances in sensibility that Dr. Aronson mentioned, but they were more of protopathic than of epicritic type, which fact might make us think that the thalamus and eventually the peripheral receptors may play a part in these disturbances. Our attention has not been called to any conditions affecting the optic nerve; therefore we have no data on the subject.

I am puzzled as to how to harmonize the conflicting remarks of Dr. Jelliffe and Dr. Rosett, the former affirming that it is well known that the cortex is not essential for the appearance of catalepsy and the latter affirming the exact opposite, that is, that the cortex is very essential. The contrast between these opinions is made more striking when we consider that de Jong and Baruk, as a result of the action of bulbocapnine in the animal scale (from those without to those with a cortex), concluded that the presence of the cortex is essential for the occurrence of bulbocapnine catalepsy. This contrast is still more pronounced when we consider Schaltenbrand's results, viz., that following the removal of the cortex catalepsy does not occur, and the results of Krause's investigation, viz., that catalepsy in acute cases is only partial, the active type of catalepsy being absent.

In view of these conflicting opinions, it was important to make an attempt to solve this very important question and we believe that our experimental methods of approach, never tried systematically before, were most appropriate ones for proving or disproving the importance of various nerve structures in the appearance of catalepsy. We must not forget that in their extensive monograph on experimental catatonia, de Jong and Baruk stressed the two following points: (1) the identity of experimental catalepsy with catatonia, and (2) the necessity of a cortical action in the production of catalepsy. These two points are refuted by our experimental work.

In regard to Dr. Rosett's remark that catalepsy appears in decerebrate animals, we may state that we are dealing with a very acute condition in which not only the cortex and the basal ganglia, but the thalamus also, are removed. Besides, no catalepsy occurs, but quite an opposite condition of extensor rigidity.

In our experiments we have investigated also the action of carbon dioxide and oxygen on the cataleptic manifestations, and we have found that animals may snap out of a cataleptic state just as well as catatonic patients do, especially when the exposure of the animal to carbon dioxide is protracted.

It is logical, as Dr. Hunt maintains, that bulbocapnine might act on the sarcoplasm of muscular fibers, and we all agree with Dr. Jelliffe's remark that bulbocapnine poisons the entire body, the muscular tissue included.

We are sorry that we have made no observations on the therapeutic manifestations of bulbocapnine, and cannot therefore answer Dr. Leiner.

THE RELATION OF THE NEOCEREBELLUM TO THE MOTOR CORTEX: AN EXPERIMENTAL ANALYSIS ON CATS AND MONKEYS. DR. J. F. FULTON.

This paper will appear in full in a later issue of the ARCHIVES.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Nov. 19, 1931

A. B. YUDELSON, M.D., *President, Presiding*

TWO BRAIN TUMORS. DR. YETTA SCHEFTEL.

CASE 1.—A white man, aged 45, a carpenter, married, in May, 1929, noticed a large cervical lymph gland on the right side of the neck. Under irradiation with roentgen rays for two months the gland became smaller. The patient then complained of pain over the right side of the face and of headache. There were ptosis of the right eyelid, double vision and poor vision.

There was a history of rheumatism for ten years. At the age of 22, the patient had sustained a severe blow on the right side of the head, but was not rendered unconscious. He claimed that partial ptosis of the right eye had been present since birth, and that his mother and grandmother also had had ptosis. One brother died of sarcoma.

In April, 1930, the patient was transferred from the department of general medicine at the Central Free Dispensary to the ocular service of the Presbyterian Hospital. He then had proptosis of the right eye, paralysis of the extrinsic eye muscles on that side, beginning papilledema, right subauricular adenopathy and headaches. One month later, he was readmitted to the Presbyterian Hospital in Dr. Bassoe's service. He complained of blindness, intense headaches, cramp-like pains all over the body, chills, sweating, numbness and tingling, buzzing in the ears, impaired hearing in the right ear and nocturia.

Physical examination revealed: bilateral amaurosis; total ophthalmoplegia of the right eye; facial paralysis; loss of touch and pain sensation over the distribution of the right fifth nerve; loss of reaction of the right masticators; optic atrophy on the right and papilledema on the left; slight nystagmus of the left eye; ptosis of the right lid, and bilateral enlargement of the cervical glands. There was paralysis of the second, third, fourth, fifth, sixth and perhaps seventh cranial nerves on the right side.

The clinical diagnosis was: inoperable carcinoma of the nasopharynx on the right, with metastatic tumor in the neck and cranial vault. The roentgenogram in April showed the sella turcica to be intact. Several months later the roentgenogram showed destruction of the floor and of the posterior clinoid process, with increased density in the sphenoidal sinus. Decompression was done in July. There followed a partial weakness of the left side with a definite Babinski sign. The patient died on Aug. 28, 1930, one year and four months after the onset of symptoms.

Necropsy revealed an ulcer as large as a half dollar in the roof of the pharynx on the right side. Extending up from this ulcer, through the soft friable sphenoid bone, there was gray, hard tumor tissue over the floor of the skull, the right temporal lobe and the right orbit. Carcinomatous metastases were present in the cervical lymph glands on both sides. The tumor was firm and irregularly spheroid, except for the lateral portion, which overhung as a flat, fungating outgrowth. Practically the whole right temporal lobe was replaced by the tumor. The diameter of the spherical part was 14 by 11 cm. The dependent portion was about 12 cm. long. The tumor was adherent to and in places penetrated the dura and adhered to some bone fragments of the skull. The tumor was pearly gray and the dependent portion a dirty reddish-brown or gray and soft.

There was evidence of molding of the cerebellum and of the occipital lobe. The convex surface of the brain showed an asymmetry of the hemispheres—the right bulged more than the left over the frontal and parietal regions.

On the right side, the third and fifth cranial nerves were embedded in tumor tissue.

On cross-section the tumor was seen to have replaced the entire temporal lobe, obliterating the sylvian fissure and compressing the right lateral ventricle. The left lateral ventricle was of normal size. The centrum ovale was also compressed on the right. The basal ganglia on this side showed softening. The cortical markings on the rest of the brain appeared normal.

Histologically, the tumor was an epithelioid carcinoma, an extension from the nasopharynx. There were irregular masses, alveoli, of epithelial cells, varying in shape and size. Between these large columns of cells was a pink-staining stroma. Tumor tissue had infiltrated the optic nerve and chiasma, and also one of the cranial nerves. Along the right side of the brain stem could be seen finger-like projections of tumor tissue infiltrating the brain tissue. Tumor cells appeared in the larger vessels especially along the longitudinal fissure.

The pons and medulla were intact.

CASE 2.—A widow, aged 53, was seen by Dr. Peter Bassoe on Jan. 6, 1929. She had no children, but gave a history of one miscarriage. During the last twelve years her weight had increased from 128 to 250 pounds (from 58.1 to 113.3 Kg.). She had complained of severe occipital headaches, nausea and vomiting since about 1925; drowsiness, dulness, poor memory and confusion had been present at times for two years. She was sometimes hard to arouse, and often had involuntary micturition and difficulty in swallowing. The menopause occurred when she was about 48 (1924).

Physical examination revealed: bilateral choked disk; pupils equal and sluggish to light; left plantar reflex normal; Oppenheim sign positive on the right; Babinski sign doubtful on the right; right ankle reflex normal, left absent; abdominal reflexes absent; arm reflexes present, and some ataxia.

Laboratory tests showed that the blood pressure was 120 systolic and 100 diastolic. The basal metabolic rate was normal. The blood sugar was 90, the calcium, 90 mg. per hundred cubic centimeters. The spinal fluid pressure was high, 14 cells. The Wassermann reaction of the spinal fluid was weakly positive. The Wassermann and Kahn reactions of the blood were negative.

The clinical diagnosis was tumor in or near the sella turcica. Operation was advised but refused.

The patient gradually became more dull and stupid, lost weight to the point of emaciation and remained in bed for several months. She died on Oct. 1, 1929.

Necropsy revealed that the brain was edematous. The dura was glistening and normal, except for one hemorrhagic area. This part had a fine membrane on the inner surface. The convex surface of the brain was asymmetrical; the left hemisphere was flattened. There was bulging over the parieto-occipital region on the left side. The distance over the parietal region, from the midline to the edge, was 8.5 cm. on the left and 6.8 cm. on the right side. The anterior portion of the frontal lobes was ragged and softened.

The tumor, weighing 600 Gm. and encapsulated, was located on the basal surface, covering the left frontal lobe and compressing it. It extended over the midline, compressing part of the right frontal lobe. The tumor was hard, nodular, round and gray, and measured 6.5 by 5.2 cm. in diameter. One removal of the tumor a hollow surface was left, and the anterior edges of the frontal lobes were thinned. The cut surface of the tumor showed near the center a few calcified nodules. The cerebellum was unchanged.

Cross sections of the brain nearest the tumor showed softening more on the left than on the right side. The asymmetry was noted on the cut surfaces. The ventricles were not distended.

Microscopically, the tumor was an endothelioma, meningioma or fibroblastoma. The whorls and calcified areas were typical. No other pathologic change was found in the brain or brain stem, except necrosis of the tissue of the frontal lobe near the tumor.

DISCUSSION

DR. PETER BASSOE: I saw both of the patients whose brains have been demonstrated by Dr. Scheftel. In the first case it was interesting that, although

we suspected a primary nasopharyngeal tumor, it was several months before rhinologists were able to ascertain by examination that such a tumor was present. I saw the second patient in consultation in the country and suspected a tumor in or near the sella turcica. After the patient's death, six months later, I received the brain, but the hypophysis had not been removed or even looked for when the brain was removed. When I saw the patient I advised that she should be brought to the city and be seen by a brain surgeon, but this advice was not taken, and the patient gradually failed mentally and physically.

CARBON MONOXIDE POISONING COMPLICATED BY MULTIPLE NEURITIS AND UNILATERAL PARKINSONISM. DR. ALFRED P. SOLOMON.

Mr. W. O., aged 29, an accountant, was overcome by the exhaust gas from an automobile while he was repairing the front tire in a private garage that received some ventilation from an open side door and large cracks in the front doors. He remained in the garage from 10:00 p. m. on Sept. 26, 1931, until 6:00 a. m. on September 27. The night was described as being very cold. When found he was cyanotic and in a deep coma. He was brought to Jackson Park Hospital, where he was under the care of Dr. Clyde E. King. A bullous lesion, about the size of a silver dollar, was noted on the left heel. He remained in deep coma for three and a half days and in a semistupor for the subsequent week. During the latter period he did not speak spontaneously, was a little resistive and answered in monosyllables only when exhorted to talk. Spontaneous involuntary movements of the left arm were noted, and examination of the left extremities caused him to give evidence of exquisite tenderness, even though he was semiconscious. The patient stated that as soon as he became aware of what was going on he was conscious of severe pain in the left hand. He first came under my care on November 2.

His complaints at that time were: excruciating pain and tenderness, numbness, tingling, pin and needle sensations and formication involving the anatomic distribution of the left ulnar and median nerves. He stated that his left hand felt as if it were not his own. The paresthesias extended to the ventral and medial surfaces of the left arm. He complained of similar but less involvement in the right hand of ulnar distribution alone. The patient was greatly disturbed by severe formication and a feeling of numbness on the posterior aspect of the left thigh. The left arm and leg felt weak and stiff, and he stated that when he stood on the left heel it felt as if the bone were devoid of flesh and were touching the floor.

His past history, habits and family history were not important.

Examination revealed a mild masked facies, rhythmic tremors of the tongue and eyelid, profuse salivation and a severe flexion contracture of the left forearm and left hand. The left hand showed evidence of hyperemia and was perspiring freely. He walked with limitation of movement of the left leg.

Objective sensory examination revealed hypesthesia to touch, pain, heat and cold of the ulnar and median distribution of the left hand, and a less marked hypesthesia of the medial half of the dorsal and ventral surface of the left forearm. There was a similar hypesthesia to all stimuli of the ulnar distribution to the right hand. The posterior aspects of the left thigh revealed anesthesia to all stimuli, which when delimited was anatomically the distribution of the posterior femoral cutaneous nerve. There was exquisite tenderness to deep pressure (which was so severe as to cause the patient to distort his face and cry out in pain) over the left hand, the left forearm anteriorly, to a less extent over the left arm, and to a greater extent over the posterior aspect of the thigh, particularly the anesthetic area, and over the left calf. The Lasègue sign was only slightly positive. There was cog-wheel rigidity of the left forearm and to a less extent of the left leg; a rhythmic tremor was noted in the left upper extremity. Examination of the deep reflexes revealed the left biceps diminished and the right biceps exaggerated. The left triceps was exaggerated, and the right triceps was normally

obtainable. The left radial and ulnar reflexes could not be obtained, and the right were easily obtainable. Both knee and achilles reflexes were exaggerated, but equal. Motor power of the flexors of the fingers of the left hand and wrist seemed slightly weaker than the right, but this could not be carefully estimated because of the marked tenderness present. I could not determine evidence of motor weakness other than that due to rigidity in the left arm and leg.

The patient has been under observation at my office since the first examination, and has shown improvement of the pallidal and striatal symptoms with the use of tincture of stramonium, and some relief from the pain and tenderness with analgesics and rest.

He shows evidence of a rather frequent carbon monoxide poisoning sequel, parkinsonism, largely unilateral, and a multiple neuritis with a rather specialized distribution. Of interest is the history of exposure to cold at the time of the poisoning, a possible correlating etiologic factor, and evidence of neuritis of a branch of a nerve directly under a bullous lesion, namely, the tibial supply to the left heel.

A Case of Carbon Monoxide Poisoning Complicated by Acute Toxic Psychosis with Catatonic Features and Later by Parkinsonism and Sensory Aphasia. Dr. Alfred P. Solomon.

A housewife, aged 30, married, from the neurologic service of Dr. George W. Hall and the medical service of Dr. Joseph L. Miller at St. Luke's Hospital, six days before admission to the hospital was taking a bath in a room in which a gas heater was burning. After an unknown period she was found unconscious on the floor. The accident happened on the first day that the natural gas mixture was used in Chicago, the importance of which is noted because the patient had previously used artificial gas without untoward effects. The pulmotor squad gave first aid for a half hour. The patient remained semicomatose for three days, and on the morning of the fourth day became conscious, so that she took food and drink, and recognized her husband. She again became comatose, but on the morning of the fifth day she was described as much better. On that afternoon the husband described her as being irrational and very irritable.

The family history, previous medical history and habits were without significance.

On admittance to the hospital the patient was semicomatose, could be aroused, seemed to understand simple commands and was very uncooperative and resistive, occasionally giving vent to a series of profane expressions which were spoken clearly and had their usual intelligible sequence. Once she was observed to have had an involuntary bowel movement while going down the corridor nude. On the next day, the prolific profanity was replaced by an incoherent, meaningless jargon which was without tendency to perseveration or clang association. The patient refused to eat, so that nasal tube feeding was resorted to, which was resisted violently. Dr. Hall described her as being exceedingly negativistic. She would not answer questions and would do the opposite of what she was told. On the seventh day after admission, the patient appeared to take some interest in her surroundings, became more cooperative and would sometimes answer questions with yes or no. It was not until a week later that the nasal feedings could be dispensed with. On November 4, Dr. Hall noted that the mental behavior was beginning to show the symptomatology of aphasia.

Neurologic examination on admission revealed: bilateral ptosis, some distention of the retinal veins, cog-wheel rigidity of the arms and legs, a positive right Hoffmann sign, unobtainable left abdominal reflex, knee jerks present but difficult to obtain, easily obtainable achilles' reflexes, positive Babinski, Gordon and Chaddock signs on the right and a suspicion of a Babinski sign on the left. The patient screamed loudly when the right leg was handled and seemed to spare voluntary movements of this extremity.

Subsequent neurologic examination revealed a more apparent striatal and pallidal syndrome, a continuance of the right pyramidal tract signs and more definite evidence that there was exquisite tenderness to deep pressure of the left arm, right arm and posterior aspect of both thighs and calves. This pain caused the patient to scream out even when she was negativistic to other stimuli. Pressure on the forearms appeared to cause no pain, and pressure on the anterior surface of the thigh did not give the same reaction as on the posterior surface. For a week before presentation the patient had been up and about, was very cooperative and cheerful, conversed with her neighbors on the ward, attempted occupational therapy, and was able to take care of all her personal needs. She was still a little apprehensive of examinations, and cried readily when pressed for an answer.

The patient has nominal aphasia. When asked to name a given object, she invariably answers, "I don't know," though occasionally she has named an object correctly. It has been possible to teach her the correct names of objects. If an incorrect name is suggested to her she adopts the suggestion as the correct name and will persist in naming it thus, even though the correct name is suggested to her later. Usually she does not seem to have insight into the correctness of a given name. If a series of articles are offered to her in sequence, she will usually name each of them by whatever name she happened to give the first. This perseveration stops only when she seems to realize that she is naming the article wrong, when she sheds tears and says, "I don't know."

She has an acalculia. She cannot add simple figures and cannot count objects correctly. If asked what $2 + 2$ is, she may give as an answer an incorrect sum, "I don't know" or "$2 + 2$ are $2 + 2$." She counted in the abstract, at a command, from 1 to 20.

Finger agnosia was apparent for both her own fingers and toes and the examiner's fingers. She correctly named the ring finger of her left hand because of a wedding ring on that finger. She can point to her eyes, nose and mouth at command.

She cannot distinguish between right and left, although she seems to understand what is wanted.

She cannot write either script or printed letters. At a command to write a word, she wrote the letter *S*, but could do no more than make encircling marks around this letter. She was told to copy a printed word, but was able to make only the first letter which was pointed in the mirror image direction and downward. She was able to read the first two words of a newspaper headline, but could read no further, repeating the first two words for subsequent words or saying, "I don't know."

The patient has an apparent amnesia for past events and poor memory for the present. She appears to be oriented for time, place and environment, but cannot so express herself.

This patient presents as a complication of carbon monoxide poisoning an acute toxic psychosis, with catatonic features, parkinsonism, pyramidal tract disease, multiple neuritis and sensory aphasia, illustrated by acalculia, finger agnosia and an inability to distinguish between right and left.

DISCUSSION

DR. VICTOR E. GONDA: I have examined these patients for the presence of a sign similar to that found in many cases of postencephalitic parkinsonism, reported previously by certain European observers (Sarbo and others). This sign, a rapid flutter of the closed eyelids of an unusually large amplitude, is present in the cases presented by Dr. Solomon.

ENCEPHALITIS DISSEMINATA: CLINICAL AND ANATOMIC REPORT OF A CASE WITH FEATURES AKIN TO MULTIPLE SCLEROSIS AND DIFFUSE SCLEROSIS. DR. JAMES C. GILL and DR. RICHARD RICHTER (by invitation).

This paper will be published in full in a later issue.

Book Reviews

Studies in Psycho-Expedition. By F. Schneersohn. Translated by Herman Frank. Price, $3.50. Pp. 222. New York: Nicholas L. Brown, 1929.

Ordinary psychology, concerning itself with abstractions and generalizations, not only has failed to bring happiness to man, but has not even succeeded in giving adequate explanations of personality and behavior. These defects the author proposes to remedy. His first chapter (entitled, "The Road to the Science of Man") views with alarm the one-sidedness of the theories of psychology and the schools of psychotherapy. He points out that none of the standard psychologic hypotheses finds a proper place for the neurotic person who, being neither sick nor well, occupies a position of undeserved uncertainty. In spite of the handicap of the illness, many neurotic persons have been pioneers in thought and action, and it is — Schneersohn believes — precisely this "nervousness" that enables these persons to plumb extraordinary depths of human emotion and to become spiritual leaders. To understand these people, one may view the problem either scientifically or intuitively. The former, in spite of its boasted rationality of method, is impracticable, for it views the individual by a single light only. It is the intuitive approach which, by virtue of its freedom and imagination, will be at once more profound and more useful. The scientific technic represents, as it were, a photograph; the intuitive, a painting. The photograph is objectively more accurate, but the painting more genuinely reflects the spiritual essence of the scene. In psychotherapy, it is only this "Science of Man" which, like the painting, grasps the spiritual totality of the problem. It is a process that requires a direct expedition into the soul and a discovery of the more remote phenomena of life, a procedure that gives it its name — psycho-expedition.

In a manner too vague and too allegoric for practical use, Schneersohn describes his method of psychic investigation. Information about the basic drives of the patient may be obtained from such sources as: simple autobiography, investigation of holiday and spare-time activities, free imaginative recollection of events long since passed and analysis of outbursts of temper or joy. Persons who find living an insipid process are suffering from what the author chooses to call "psychic scurvy." Just as a diet may be so one-sided as to result in a deficiency disease, so psychic life may be so lacking in significant stimulating influences that the patient finds the routine of life an uneasy and unhappy one. This deficiency in vital interest (after the pattern of clinical medicine) is termed "psychic scurvy." That this is, in a sense, but a restatement of the obvious, Schneersohn admits; but, he insists, we need courage to be simple, and vision to adhere to the obvious.

The energetic, extroverted person is renamed a "spherical personality." The intensity of interest in life manifested by such a person is measured inversely by a "spherical quotient"; that is, the extroverted man to whom life seems tedious has a high spherical quotient. Escape from such tedium takes the form of regression to a deeper mode of psychic existence. Three such modes are presumed to exist: (1) normal, (2) intimate and (3) primitive. The normal represents ordinary consciousness and is exemplified by daily rational activities. The intimate mode is associated with emotional urge and with a tightening of affective tension. Religious prophecy and artistic inspiration represent activities of this intimate sphere. The primitive mode is the deepest substratum of psychic life as evidenced by dreams, hypnosis or mental disease. In a civilized community, for example, cannibalism may be practiced in an emergency — an instance of the upward thrust of the primitive mode. The clinical value of this classification is in the understanding of certain neurotic practices. When life does not afford enough of interest to allow intimate modes free play, the patient falls back into the activities of the primitive sphere. Nervousness and suicide may be understood as such rebellions against the tedium of life; debauchery as a reaction against the emptiness of daily vital activities.

In the chapter carrying the bizarre title "Psychical Man Therapy and Man Hygiene," the author outlines a plan of healing by methodical restitution of equilibrium between psychic longings and actual ways of living. Among the methods are: change in the curriculum of life, discovery of the real psychic urges and courage enough to make such modifications of living routine as are needed to satisfy these urges.

In his foreword to the book, John Dewey praises Schneersohn's attempt at integration rather than analysis; he expresses approval of the author's emphasis on the artistic or intuitive point of view. Adolf Meyer, in a second foreword, suggests that this artisticness of outlook is a desirable counterbalance to present-day mechanistic philosophy. Meyer also likes the author's stress on deficiency rather than inferiority as a basis for psychoneurotic manifestations.

The book, on the whole, seems to be but a mystical elaboration of some of the well known facts of every-day psychotherapy.

Amusie. By Erich Feuchtwanger. Price, 26 marks. Pp. 292. Berlin: Julius Springer, 1930.

This monograph covers thoroughly the subject of amusia. It begins with a report of two cases, one of predominant sensory amusia, the other of expressive amusia. Feuchtwanger is careful to separate from his subject the paramusias that occur as a result of middle or inner ear diseases. He discusses adequately the central anakusias or hearing disturbances that are due to injury of both temporal lobes in the region of Heschl's convolutions, or to the fiber systems connected with them. Partial anakusias are possible, just as it is possible to get partial hemianopias from disturbances of the visual sphere. Feuchtwanger draws a strict line between the central auditory disturbances and the acoustic-gnostic disturbances of a musical sort. He discusses fully the question of sensory amusia. In his discussion of this subject, he draws an essential distinction between the acoustic sensory sphere and the acoustic formative sphere. The one has to do with the differentiation of noises, tone and the like, as to intensity and quality, while the other has to do with the organization of music into melody, and its organization into rhythm and tempo. It is a mnestic function. Disturbances of this function may be manifested by: (1) disturbance in acoustic perception, an inability to recognize the organization of the musical picture in the presence of an intact sensory structure; (2) disturbances in form and structure in the formation of a musical score; (3) disturbances in tonal structure, as in an inability to arrange musical structure or the tonal system, and disturbances in transposition; (4) disturbances in rhythm, both with and without loss of appreciation of tact and tempo, and (5) disturbances of musical memory in the narrow sense.

The expressive or motor amusias are divided roughly into two groups: (1) the constructive-musical agnosias, in which there is inability to form musical pictures by any means, with the presence of an intact sensory sphere, and (2) the expressive-musical disturbances of a dyspraxic nature. This is really only one expression of an outfall in the sensory sphere or of an apraxia.

Feuchtwanger discusses thoroughly the question of amusia and speech. He comes to the conclusion that it is not possible to postulate a separate localization for speech and music in the sensory area of the auditory field in the cortex. He states further that in the cases of pure sensory aphasia that have been reported, in which music has been investigated, there is no case that proves the separation of music and speech. In the majority of cases of aphasia there are disturbances of music in addition to those of speech. In cases in which there is no amusia the speech trouble is more likely to be in the understanding of the significance of speech rather than in the appreciation of speech sound.

The monograph is a thorough and complete study and an important contribution to the whole subject of amusia. It is an indispensable volume for those who are interested in aphasia and speech disorders of any sort. It can be recommended highly.

Theodor Meynert und seine Zeit. By Dora Stockert-Meynert. Price, 5.30 marks. Pp. 297. Leipzig: Österreichischer Bundesverlag, 1930.

In this book the daughter of Theodor Meynert gives her reminiscences of her parents and the social and university setting in which they moved. The result is not so much an account of the medical and scientific work of the period as a story of a young girl's growing up in the home and times of Theodor Meynert. The memories of the personalities and events of the garden of the asylum, and later of the private home of the family, the contacts and anecdotes of the more humble and the more illustrious members of the home and university, and of the artistic, literary and cultural Vienna of the late seventies and eighties up to 1892 are offered as they figured in the reminiscing of an interested and observant daughter of a man prominent in the intellectual life of the time. Here and there, in the midst of reminiscences of a general nature, some items of significance in the personal life of well known personages give material illustrations of the medical life of the day—Meynert's laboratory and contacts, Rokitansky, and the Viennese school of physicians and teachers. Of special interest is the correspondence, especially the correspondence between Meynert and Billroth in their last days. An index of the personages facilitates a reference to the characterizations, sidelights and events which in the text appear as incidents, and more as supplements of a diary or life-history of the charming authoress than as a systematic account of a historian. Here and there an incident in the medical history of noted men comes up—such as the fact that Meynert was offered the Zurich chair of psychiatry before Forel was selected, and many incidents of congresses, etc. As a simple and intimate account of the events of those interesting days the book will revive many memories in those who knew the Vienna of the period, and here and there it will clear up human relationships hardly otherwise recorded. Taken in the spirit in which it is written, the book makes one feel grateful for the preservation of the many impressions of a nonprofessional but culturally stimulating and provocative personality. Meynert was indeed the central figure of a remarkable epoch of psychiatry which forms a striking background for the later developments of the Vienna schools—for Vienna, like most European centers, was and is much more than a one-man center.

Sex in Marriage. By Ernest R. Groves and Dr. Gladys Hoagland Groves. Price, $3. Pp. 248. New York: The Macaulay Company, 1931.

"Sex in Marriage" is a book that is well written and well considered; it represents, obviously, a wide and intimate experience concerning the successful as well as the unsuccessful connubial life, and gives a sensible conception of marriage and what leads up to it. It steers clear of the exalted vocabulary that makes a cult largely of sex stimulation and of an obligatory sex perfectionism and ars amatoria. On the other hand, it pays much attention to frequently neglected misunderstandings. Yet it seems regrettable that in these days it still should be impracticable to offer in one book the good sense and the good practice also on matters that remain under legal tabu. The burning question after all is that of conception, and of the sex urge with and without procreative urge. To the reviewer's knowledge, the balancing of sex urge and safety and the preoccupations connected with contraceptive matters lead to far more hazards of misunderstandings and complications than any other factor of trouble. Another issue might be that of flirtation and sex arousals apt to disturb the sense of unquestioned affection and "belonging."

The book deserves an index. After all, however attentive and thorough one's reading may be, still one often feels that one would like to refer again to certain topics if only there were at hand a serviceable index to guide to the relevant passages.

The authors are rendering a real service to the American public through their readable presentation of the fruit of their studies. They contribute a great deal toward a sense of the practicability of giving marriage advice, which is not as

yet safe when left to the average physician, who has neither the time nor the actual experience with social problems, and especially if he has not a keen sense of the need of going into very individual and specific detail without which one often stirs up more than one helps.

This book, together with the other pertinent writings of the authors, deserves a wide circle of readers.

The Mind at Mischief: Tricks and Deceptions of the Subconscious and How to Cope with Them. By William S. Sadler. With Introductions by Robert H. Gault and Meyer Solomon. Pp. 400. New York: Funk & Wagnalls Company, 1929.

In his preface the author asserts that a number of excellent books have been helpful to the layman in his effort to understand himself psychologically, and that there is an abundant literature on the psychoses for the professional reader; "but practically nothing has been written on those cases of abnormal psychology which occupy a middle ground between these two groups." It is this gap that the author has endeavored to fill in this volume, which he will place "in the hands of a patient — or of his friends." The book itself shows the consequences of such an effort; it is neither scientific nor suitable for a layman. One can see little of value, for instance, in such statements as a claim for direct opposition to the "teachings of Freud," in that Sadler finds "one may not only suppress sex thoughts which interfere with the religious ideals, but one may also come to the place where he suppresses religious conviction so as to give more free expression to sex emotions." The book teems with such remarks, often illustrated by superficial analyses of case histories. While there are some clear expositions of emotional conflicts and mechanisms, the book cannot be recommended as filling satisfactorily any particular need.

A Doctor of the 1870's and 80's. By William Allen Pusey. Price, $3. Pp. 153. Springfield, Ill.: Charles C. Thomas, 1932.

So well has the author described the professional life of his father, Dr. Robert B. Pusey, of Elizabethtown, Ky., between the years 1870 and 1889, that the reader becomes at once envious and wishes that the modern encumbrances of practice such as the telephone, office buildings and the automobile had never been invented. The general practitioner in those halcyon days practiced more or less at his leisure, although it at once must be admitted that it was a hard life. How pleasant it must have been to saddle your particular pet horse or a horse and buggy and to enjoy the scenery instead of having to be careful of the automobile mortality rate. There is much more fun in taking pride in your stable and your buggy than in the type of car that you are driving. Moreover, from the practical standpoint more income was to be made then than now, for the charges for services, strange as it may seem, were not any smaller than they are now. For example, a visit in town or an office call was a dollar and upward; consultation, from $5 to $25, usually $10. His income from 1870 to 1886 averaged $5,200 a year. As the author well states, this is equivalent to about two and a half times that sum at the present time in the same kind of small town.

One of the interesting things that the depression has shown is that of all the professions, from the income standpoint, the medical profession is more fool proof than most, certainly more than those of law, architecture and the various trades, and of the medical profession perhaps the general practitioner has suffered less than the specialist. In fact, the depression has shown that the sick can do without physicians to an astonishing degree without suffering very much from this deprivation.

Experimental Social Psychology. By Gardner Murphy and Lois Barclay Murphy. Price, $3.50. Pp. 709. New York: Harper & Brothers, 1931.

The purpose of this book is to show what the experimental approach to the understanding of social behavior of human beings has yielded and what it may

rightfully be expected to yield. There is no doubt that the authors have fully accomplished their purpose, for it is at once a sane, if not too long, presentation; there are 709 pages.

It is divided into three parts headed: "Basic Principles," "A Genetic Study of Social Behavior" and "General Laws of Social Interaction in Our Own Society." At the end of each chapter there are a bibliography, an author's index and a subject index. The book is too long for review. It is, however, welcome for its sanity and the completeness of its presentation.

An Introduction to Neurology. By C. Judson Herrick. Fifth edition. Price, $3. Pp. 417. Philadelphia: W. B. Saunders Company, 1931.

The fifth edition of this well known work differs from those preceding only in that the chapters on the neuron, reflex circuits and general physiology of the nervous system have been entirely rewritten, and all the text has been carefully revised in the light of current research. There is no work in any language that comes up to this small book as an introduction to neurology, and it is to be highly recommended to students in neurology.

A Brief History of Medicine in Massachusetts. By Henry R. Viets, M.D. Price, $4. Pp. 184. Boston: Houghton Mifflin Company, 1930.

This book is one of the signs of the increasing interest in the history of medicine and, indeed, in the history of culture that is taking place in this country. At one time there was a strong tendency on the part of all young physicians to believe that medicine began about twenty years ago, and that nothing that occurred before then was of any value. There was an underlying belief among such students that intelligence and knowledge are of this day's growth. This led to narrow mindedness and was a great evil.

Viets's "History of Medicine in Massachusetts" is in itself an interesting book and will help to spread the great truth that all science has its roots in the early history of man. The book should be read by everyone who is interested in the history of medicine. It is carefully written, accurate in statement and not provincially boastful.

The Principal Nervous Pathways. Neurological Charts and Schemas with Explanatory Notes. By Andrew Theodore Rasmussen, Ph.D. Pp. 73. New York: The Macmillan Company, 1932.

The reviewer, in common with all teachers of neuro-anatomy and neurophysiology, has always found wanting a particular chart or charts for the purpose of clear elucidation of the subject, for no matter how many charts one may have some particular fiber connection can never be shown. If there was only some way to show the motor system, for example, as an active, live, functioning structure, teaching of this subject would become infinitely easier, and the students would be able to get just the shade of meaning that the teacher tries so hard to portray.

This book consists of twenty-eight charts and schemas of the nervous system. They are excellent. If there is any criticism it is in the fact that they attempt to portray too much, but then, as the author states in his preface, too many legends are better than too few. All teachers of this subject will no doubt be grateful to the author for his efforts.

Gehirnpräparation mittels Zerfaserung. Anleitung zum makroskopischen Studium ges Gehirns. By Dr. J. Wilhelm Hultkrantz. Price, 6.60 marks. Pp. 35. Berlin: Julius Springer, 1929.

This small pamphlet with forty-four photographs gives a graphic idea of the author's method of study of the gross anatomy of the brain by defibrillation. The technic is carefully described, and consists of separation of the various tracts in

the hardened brain by blunt dissection, or what the author calls "Zerfaserung" or defibrillation. One can get an excellent idea of the various pathways in the brain by this method. The idea of studying the hardened brain by this means is not new, and the author claims no originality for it, but he has perfected the method. This small booklet is an excellent one for students of brain anatomy, neurologists and laboratory workers. The printing is clear and the illustrations excellent, as in all of Springer's publications.

A Text-Book of Clinical Neurology. By Israel S. Wechsler, M.D. Second edition. Price, $7. Pp. 759. Philadelphia: W. B. Saunders Company, 1931.

This second edition is a considerable improvement over the first, for some of the errors that always creep in in the first edition have been eliminated. Advances in the current knowledge of such diseases as tumors of the brain and epilepsy have been added. The subject of encephalography has been elaborated. The classification originally used has been maintained, although shifts have been made here and there which have clarified the subject. Altogether it is one of the best and sanest small books on clinical neurology, and can be recommended to students and general practitioners.

Die Lebensvorgänge im normalen Knorpel und seine Wucherung bei Akromegalie. By J. Erdheim. Price, 18 marks. Pp. 160. Berlin: Julius Springer, 1931.

This monograph by Erdheim is a thorough study of the changes to be seen in cartilage in acromegaly, the rib being used as the unit of study. The first part of the monograph is concerned with the normal histology of the rib cartilage, followed by an intensive study of the cartilaginous changes to be observed in the rib cartilage in acromegaly. The study is well illustrated, and the changes noted are described in detail. It is recommended highly to those interested in the subject.

The Diagnosis of Nervous Diseases. By Sir James Purves-Stewart. Seventh edition. Price, $11. Pp. 730. St. Louis: C. V. Mosby Company, 1931.

When a book has reached its seventh edition in a period of twenty-five years, it admittedly must have merit. The present edition does not differ much from the last. It is slightly larger, because the whole work has been reset, and many illustrations have been added. It differs from the ordinary textbook in that the diagnosis of nervous diseases is emphasized, and it can be recommended to students and general practitioners.

The Doctor in Court. By Edward Huntington Williams, M.D. Price, $3. Pp. 289. Baltimore: Williams & Wilkins Company, 1929.

In a readable and entertaining book the author has described the usual and unusual experiences of "the doctor in court." The author has drawn not only on his own experiences but on those of others, and illustrates at length the various points that come up in such practice by apt references to well known trials.

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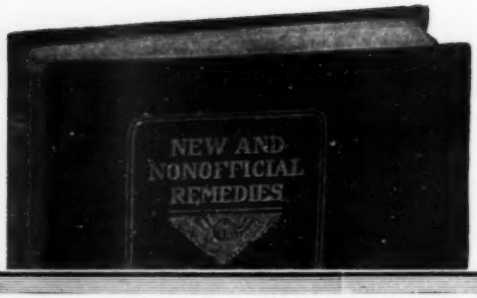

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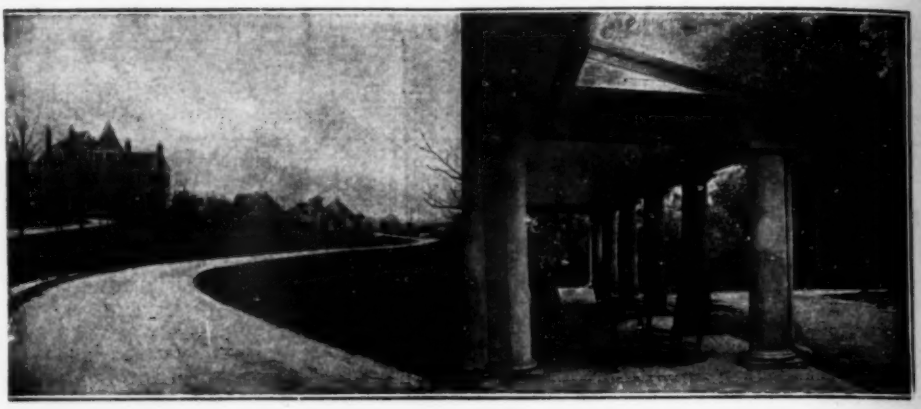
AMERICAN MEDICAL ASSOCIATION, 535 N. Dearborn St., Chicago

JAS. K. HALL, M.D. O. B. DARDEN, M.D., Associate P. G. HAMLIN, M.D., Associate PAUL V. ANDERSON, M.D.

Westbrook Sanatorium

RICHMOND, VIRGINIA



The sanatorium is a private institution of 135 beds, located in the Ginter Park suburb, midway between trolley lines, within ten minutes ride of the heart of the city, and on the Richmond-Washington National Automobile highway. Midway between the North and the distant South, the climate of this portion of Virginia is almost ideal. Nearby are many reminders of the civil war, and many places of historic interest are within easy walking distance.

The plant consists of twelve separate buildings, most of which are new, located in the midst of a beautifully shaded fifty-acre lawn, surrounded by a hundred and twenty-acre tract of land. Remoteness from any neighbor assures absolute quietness.

The large number of detached buildings makes easy the satisfactory and congenial grouping of patients. Separate buildings are provided for men and for women. Rooms may be had single or en suite, with or without private bath. A few cottages are designed for individual patients.

The buildings are lighted by electricity, heated by hot water, and are well supplied by baths. The water supply for the entire institution is derived from an artesian well on the grounds, of approved therapeutic value.

The scope of the work of the sanatorium is limited to the diagnosis and the treatment of nervous and mental disorders, alcoholic and drug habituation. Every helpful facility is provided for these purposes, and the institution is well equipped to care for such patients. It affords an ideal place for rest and up-building under medical supervision. Five physicians reside at the sanatorium and devote their entire attention to the patients. A chartered training school for nurses is an important part of the institution in providing especially equipped nurses—both men and women—for the care of the patients.

Systematized out-of-door employment constitutes an important feature of the treatment. Wonderful work in the arts and crafts is carried on under a trained teacher. There are bowling, tennis, croquet, billiards and pool.

The sanatorium maintains its own truck farm, dairy and poultry yard.

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