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INTRASPINAL LIPOMAS

REPORT OF CASES; REVIEW OF THE LITERATURE, AND CLINICAL AND PATHOLOGIC STUDY

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Masses of adipose tissue within the cranium and within the spinal canal not associated with bifid spines are rare. Intracranial lipoma, reported cases of which numbered 74 up to 1936 (Sperling and Alpers [1]), rarely produces clinical symptoms because of its small size, and no reported tumor of this sort had been attacked surgically. Intraspinal lipoma is even less common, but it frequently grows to enormous size, produces compression of the spinal cord and is surgically exposed. When it is encountered, its true nature is unsuspected until the yellow mass is visualized or, when the tumor is reddish or white, until histologic examination is made. Elsberg's [2] series of data on 267 cases of extramedullary tumors, compiled in 1941, included 6 instances of lipoma. It is probable, however, that the 2 tumors lying both intradurally and extradurally were associated with spina bifida, since Wolf,[3] in discussing what appears to be the same series of tumors, omitted them and noted that 1 of the 3 intradural tumors was associated with spina bifida. With the omission of these 2 tumors, lipomas constitute 1.5 per cent, or less, of extramedullary tumors. Steinke [4] reported data on 330 cases of tumors of the spinal cord collected from various sources. Among these cases were 4 instances of lipoma and 2 of angiolipoma (1.8 per cent). Von Lennep [5] tabulated data on 153 cases of tumors of the spinal cord from one clinic and included 2 cases of lipoma. Among 740 verified cases of tumors of the spinal cord data on which are in the files of the Mayo Clinic up to December 1942, there are 6 instances of lipoma (0.8 per cent). An additional tumor recently discovered brings the percentage to about 0.9. The over-all incidence appears to be close to 1 per cent of all primary intraspinal neoplasms.

The problem of which tumors to exclude as being merely masses of fat misplaced because of spina bifida has been handled differently by different authors. Spiller [6] included 3 cases which others, including us, would exclude because of an isthmus linking the intraspinal lesion with an extraspinal lipoma through a variety of bony defects. Other investigators (Wolbach and Millet [7]; Sachs and Fincher [8]) would discard the case of myolipoma reported by Gowers [9] because it is assumed that any tumor-bearing muscle must have come from the outside, despite the fact that no spina bifida

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3. Wolf, A.: Tumors of the Spinal Cord, Nerve Roots and Membranes: II. Pathology, in Elsberg, C. A.: Surgical Diseases of the Spinal Cord, Membranes, and Nerve Roots: Symptoms, Diagnosis, and Treatment, New York, Paul B. Hoeber, Inc., 1941, p. 349.

4. Steinke, C. R.: Spinal Tumors: Statistics on a Series of 330 Collected Cases, J. Nerv. & Ment. Dis. **47**:418-426 (June) 1918.

5. von Lennep, H.: Ueber Rückenmarkstumoren, Deutsche Ztschr. f. Chir. **160**:137-140 (Nov.) 1920.

6. Spiller, W. G.: Lipoma of the Filum Terminale, J. Nerv. & Ment. Dis. **26**:287-296, 1899.

7. Wolbach, S. B., and Millet, J. A. P.: Diffuse Sub-Dural Lipomatosis of the Spinal Cord in an Infant, Boston M. & S. J. **168**:681-682 (May) 1913.

8. Sachs, E., and Fincher, E. F.: Intramedullary Lipoma of the Spinal Cord: Complete Operative Removal, Arch. Surg. **17**:829-833 (Nov.) 1928.

9. Gowers, W. R.: Myo-Lipoma of the Spinal Cord, Tr. Path. Soc. London **27**:19-22, 1876.

	Year	Author	Sex	Age at Onset of Symptoms	Duration	Level	Position on Cord	Traversing Roots
1	1876	Gowers [9]	..	.....	.....	Conus	Lateral half	Anterior and posterior; posterior roots more disorganized
2	1884	Braubach [28]	F	14 mo.	4 yr.	C5 to T4	Right posterior surface	None
3	1888	Turner [23]	F	42 yr.	12 yr.	Midthoracic portion of cord	Left side	Present
4	1899	Spiller [6]	F	.....	.....	Filum terminale	.....	Present as small bundles separate by fat
5	1906	Root, E. F., cited by Bucy and Gustafson [20]	F	28 yr.	15 yr.	Midthoracic portion of cord	.....	.....
6	1912	André-Thomas and Jumentié [33]...	M	.....	.....	L5 to S5	Posterior	Present
7	1913	Wolbach and Millet [7].....	M	Birth (?)	10 mo.	Entire cord; cauda equina	Posterior	Present
8	1918	Oppenheim and Borchardt [19].....	M	31 yr.	13 yr.	C1 to C4	Midline posterior	.....
9	1920	Ritter [18].....	M	40 yr.	3½ mo.	C1 to T1	Right posterior	Present, greatly infiltrated and subdivided by fa
10	1921	Henneberg [35].....	..	.....	.....	Cervical portion of cord	Midline posterior	Absent (?)
11	1925	Elsberg [24] †.....	F	17 yr.	5½ mo.	C8 to T2	Lateral surface, anterior to dorsal roots	None
12	1925	Elsberg [24] ‡.....	F	19 yr.	3 mo.	T2 to T4	Lateral surface, anterior to dorsal roots	None
13	1927	Stookey, B.: Am. J. Dis. Child. **36**: 1184-1203 (Dec.) 1928	M	1? yr.§	10 yr.	C2 to T5	Posterior: more to the right (?)	Present
14	1927	Bielschowsky and Valentin [31].....	M	Birth (?)	1 yr.	T11 to S4	Posterior	Present
15	1928	Sachs and Fincher [8].....	M	43 yr.	3 yr.	T7 to T8	Midline posterior	None
16	1928	Fay [27] ¶.....	F	21 yr.	2 mo.	T3 to T7	Posterior	Present
17	1928	Beykirch [34].....	M	33 yr.	3 yr.	Cauda equina	.....	Present
18	1931	Kernohan, Woltman and Adson [14]	M	11 yr.	8 yr.	C4 to T1	Midline (?)	.....
19	1935	Eckart [29].....	F	24 yr.	6 yr.	Midcervical to lumbar	.....	.....
20	1935	Stotz, in discussion on Fischer, D. W.: Zentralbl. f. Chir. **62**: 2970 (Dec. 14) 1935	..	.....	.....	.....	.....	.....
21	1936	Dobrokhotoff, cited by Jabotinski,[22] and Kouraeff, cited by Jabotinski [22]	F	24 yr.	1½ yr.	Cervical to lumbar	.....	.....
22	1936	Scherer [25].....	F	40 yr.	1½ yr.	C4 to T5	Right dorsal root line	Present and widely separated by fat
23	1937	Guillain, Bertrand and Salles [26]...	F	42 yr.	10 yr.	T5 to L5	Entire dorsal surface	Present and widely separated by fat
24	1938	Bucy and Gustafson [20].....	M	1-2 yr.?	17 yr.	C1 to C4	Posterior	?

* This information is taken from the report by Bucy and Gustafson.[20]
† This is the sixth case of extramedullary tumor to be reported and is described on page 29 of Elsberg's book.[24]
‡ This is the eighth case of extramedullary tumor and is described on page 39 of Elsberg's book.[24]
§ A history of weakness dating back to 1915 was given to other physicians in 1919, when the patient was 3½ years of age. The patient must have been born in the latter part of 1915 and the weakness noted shortly after.

Connective Tissue	Spinal Puncture	Roentgenographic Evidence	Other Disorders	Operation
Capsule of pia; excessive fibrous tissue where tumor attached to cord; extensions into cord not prominent	.....	.....	Tabes.....	Necropsy
Proliferation of stroma with extensions into cord; increased nuclei	.....	.....	.....	Necropsy
Pia thickened and cellular; cellular fibrous tissue sending strands into cord	.....	.....	Obesity.....	Necropsy
No invasion of filum.....	.....	.....	Tabes.....	Necropsy
No extensions into cord....	.....	.....	.....	Tumor removed; improvement; death two years later, of pneumonia *
Invasion and destruction of cord by fibrous tissue	.....	.....	.....	Necropsy
Benign fibrous extensions into cord; increased vascularity	.....	.....	*Intracranial lipoma;* hydrocephalus; absence of right kidney; harelip	Necropsy
Lipomatous and "sarcomatous" extensions into cord	.....	.....	.....	Subtotal removal of tumor; patient still helpless
Pial septum between tumor and cord, sending cellular strands into cord; embryonic fat forming new lobules; liposarcoma (?)	.....	.....	Kyphoscoliosis; hydrocephalus	Necropsy
Lamina of connective tissue next to cord; heavy strands penetrating cord; "proliferated endothelium"	.....	.....	.. ..	Exploration (?); necropsy
Some of cord substance came away with tumor; some extensions into cord (?)	Fluid xanthochromic; globulin present	Kyphosis and arthritis	.....	Two stage removal; patient walking four years later
Stroma much more cellular in one photomicrograph than in the other	Fluid xanthochromic; globulin present	.....	.....	Total removal in two stages; complete recovery
Minimal amount in specimen removed	Almost complete block; fluid xanthochromic; globulin high	Spinal canal widened (C3 to T3)‖	Subcutaneous lipoma over intraspinal lesion	Partial removal; some improvement three years later, then recurrence *
Thickened pia sends heavy processes into cord	.....	.....	Hydrocephalus; hydromyelia; clubfeet; pseudohermaphroditism; cataracts	Necropsy
Dense capsule with minimal stroma	Normal fluid; steppage type of fall of pressure	Spine normal; picture after injection of iodized oil suggestive	.....	Total removal; death eight years later of unknown cause *
Tumor fibrous; superficial "invasion" of cord	Fluid xanthochromic; protein increased; no block	Spine normal	.....	Capsule incised; death in three months
Minimal stroma with few nuclei	Nonne reaction positive	Descent of iodized oil held up at T11	Conus abnormally high	Partial removal; improvement
Minimal stroma with few nuclei	Fluid xanthochromic; globulin present; slow fall of manometric pressure	.....	....	Partial removal; complete recovery; recurrence nine years later
Fibrous regions	.....	No block to ascent of iodized poppyseed oil	.....	Necropsy
Fibrolipoma with destruction of whole thickness of cord	.....	No block to ascent of iodized poppyseed oil	....	Necropsy
... .	Tumor diagnosed by this test, but results unknown	.....	.....	Partial removal twice with benefit; death from meningitis after third operation; necropsy
Capsule of pia; fibrous proliferation of perineurium where roots enter cord	.....	*Spine normal*	.....	*Necropsy*
Fibrous tissue infiltrated and dorsal columns destroyed	220 mg. of protein per 100 cc.	.....	.....	Necropsy
Dense capsule; light stroma	Albumin content normal; reaction for globulin positive; no block	Spinal canal widened from C1 to C3; complete block (to ascent) of iodized poppyseed oil at C4	Umbilical hernia; pilonidal cyst; lipoma of neck over deep lesion	Subtotal removal; excellent result

‖ The roentgenogram included in the definitive report shows widening of the vertebral canal from at least the fifth cervical to the third thoracic vertebra. In another paper (1928) a different roentgenogram is shown, in which the pedicles are shown to be affected as high as the *third cervical vertebra.*

¶ This is apparently the same case as that reported in more detail by Wilson, Bartle and Dean,[42] though they did not indicate this.

TABLE 1.—*Data on Twenty-Nine*

	Year	Author	Sex	Age at Onset of Symptoms	Duration	Level	Position on Cord	Traversing Roots
25	1938	Baker and Adams [20]	F	Birth (?)	1 yr.	Entire cord	Posterior	?
26	1939	Jabotinski [22]	F	3 mo.	13 yr.	C1 to C8	Left dorsal surface	Present
27	1944	Case 2, this series	F	19 yr.	1 yr.	T7 to T11	Posterior	Present and widely separated by fat
28	1944	Case 3, this series	M	41 yr.	2 yr.	T9 to T10	Right dorsal roots	Hypertrophic and disorganized
29	1944	Case 4, this series	M	18 yr.	4 yr.	T6 to beyond C7	Right posterior (?)	.....

was described by Gowers. In the collected cases and in the case reports to follow there is no instance of spina bifida.

Because of the special causation of lipomas in the intradural region occasioned by the paucity of fat in this location, as contrasted with lipomas in the extradural situation, where fat is abundant, because of the structures within the dura likely to become involved in the tumor while this membrane obviates such a possibility in the case of tumors outside it and because it is the classic practice to make the separation of intradural and extradural tumors the first step in clinical classification, the intradural lipomas will be considered apart from the extradural lipomas and the corresponding features of the two types will be harmonized later.

INTRADURAL LIPOMA

The total number of cases of intradural lipoma reported in narrative form is only 26. An additional 10 or 12 cases have been merely tabulated in reports of series of tumors. Table 1 lists in chronologic order the cases previously recorded, together with the cases reported in this paper. The essential features of each case may be gathered from table 1, without the necessity of our giving a narrative description of each one.

Frazier and Allen [10] tabulated 4 cases of intraspinal lipoma, in 2 of which the growth was intramedullary in the cervical region and operation was performed, occurring in a series including cases from the literature and personal cases as of May 1915 (according to Steinke,[4] who collected the cases and made a separate report). Since no such cases had been reported by other authors prior to this publication, these 2 cases must have occurred in the personal experience of Frazier and Allen and never have been reported elsewhere. Since nothing is known of these cases, they are not included in the tabulation.

Von Lennep [5] had 1 instance of intradural lipoma among the cases which he reported in tabular form, but he gave no details and we do not include it.

Schmieden and Peiper [11] described an intramedullary tumor of the spinal cord which other authors have accepted as a lipoma but which will not be so considered here. The tumor was devoid of pial connection, was soft but solid and had the gross appearance of adrenal gland tissue. When it was cut across, multiple minute bleeding points were observable on the cut surface. It consisted of densely packed round and oval cells containing many small droplets of doubly refractile fat and was stated to be a lipoblastoma. It is our opinion that the true nature and proper designation of this lesion was hemangioendothelioma. The tumor did not contain adult fat cells—only cells with fat in droplets, which are seen so abundantly as the "pseudoxanthoma cells" of hemangioendothelioma. The multiple bleeding points, caused by release of the blood contained within the small blood spaces of the hemangioendothelioma, are characteristic of such a tumor.

According to Antoni,[12] Foerster stated in a personal communication that he had encountered 3 cases of intramedullary lipoma, but no details are known.

10. Frazier, C. H., and Allen, A. R.: Surgery of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918.

11. Schmieden, V., and Peiper, H.: Ueber ein erfolgreich operiertes endomedulläres Lipom des Halsmarks, nebst einigen Bemerkungen zur Chirurgie der intramedullären Tumoren, Deutsche med. Wchnschr. **55**: 513-516 (March 29) 1929.

12. Antoni, N.: Tumoren des Rückenmarks, seiner Wurzeln und Häute, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 14, pp. 1-131.

Connective Tissue	Spinal Puncture	Roentgenographic Evidence	Other Disorders	Operation
Dense membrane separating tumor from cord; some small and actively growing cells	.....	.....	Absence of iris; hydrocephalus; intracranial lipoma; defect of left temporal bone; xanthoma of eyelids	Necropsy
Fibrous tissue proliferated and sending extensions into cord	.....	.....	.....	Necropsy
Connective tissue of roots hyperplastic at dorsal root origin; extensions into cord	120 Gm. of protein per 100 cc.; no block	Left pedicles from T5 to T9 thinned; backs of bodies of vertebrae T5 to T8 eroded	.....	Partial removal; no improvement
Heavy septums bearing roots	100 mg. of protein per 100 cc.; no block	Pedicles of T11 eroded; descent of iodized oil obstructed at T10	Obesity; pilonidal cyst; extradural lipoma on right root at T9	Total removal
Lipoma slightly fibrous....	120 mg. of protein per 100 cc.; 11 cells per cu. mm.; partial block	Pedicles of vertebrae T3 and T4 eroded; more on right side than on left	.....	Laminectomy without removal

Jaeger[13] appears to have reported a case recently, since a title suggestive of such an observation is listed in the *Quarterly Cumulative Index Medicus*. The foreign journal in which Jaeger's paper appeared no longer reaches the Mayo Clinic library, however.

Additional data on 4 cases of intradural lipoma observed at the Mayo Clinic (cases 18, 27, 28 and 29, of table 1) are given in the following paragraphs.

REPORT OF CASES

CASE 1.—A Jewish youth aged 19 years registered at the clinic on July 10, 1927, complaining of numbness of the legs and the left hand, weakness of the arms and legs, pain in the neck and difficulty with urination. This case was mentioned previously by Kernohan, Woltman and Adson[14] and by Adson.[15]

The family history was of no consequence, but the previous medical history was of possible significance. At the age of 5 or 6 years the patient had fallen down a flight of twenty-four steps and injured his neck in an unspecified manner. Gradually increasing low cervical pain followed this injury. Cervical traction for six months had given relief, and a brace to the neck was worn for the next year. At the age of 8 years a bone graft had been performed on the cervical portion of the spinal column for what was stated to be tuberculosis.

A three or four year period of fair health followed, and it was not until the age of 11 or 12 that neurologic symptoms began. The first sign noted was clumsiness in walking, and it was thought at the time that the left leg was most affected. After an unspecified time the legs began to drag and the arms became weak. A year later there was onset of a recurring low cervical pain, which lasted only a month or so out of the year, but appeared yearly for six years. Three months before the patient came to the clinic the pain had begun again but failed to disappear as before. This pain was usually a dull ache over the low cervical spinous processes, with occasional extension to the left shoulder, but sometimes it was throbbing. At the age of 15 years the weakened arms became awkward. At the age of 18 atrophy of the hands was noted, the right leg became much weaker at the hip and numbness was felt from the waist down. In March 1927 some sort of operation had been performed on the neck, without influencing the course of the disease. During the month preceding the patient's registration at the clinic numbness of the fingers of the left hand and a rapid increase of all symptoms developed, together with difficulty in starting the flow of urine.

The physical examination, aside from the neurologic portion, gave essentially normal results. The patient walked with a spastic gait. Below the second thoracic dermatome there was total absence of appreciation of painful, thermal, tactile, joint and vibratory stimuli except that the back of the left thigh and calf retained slight cutaneous sensibility. Joint and vibratory sensibilities were diminished slightly in the hands, and there was moderate diminution of appreciation of pain and touch in the ulnar distribution of both hands. Considerable weakness of the finger flexors and the intrinsic muscles of the hand was apparent, being more severe on the left side. The legs were weak and spastic. The biceps reflex was normal, but the triceps reflex was notably diminished on both sides. A Hoffmann sign was elicited on the left side. The patellar and achilles reflexes were exaggerated, being stronger on the right side than on the left. The presence of ankle clonus and the Babinski sign bilaterally completed the picture.

Lumbar puncture revealed xanthochromic fluid, in which there was globulin. The manometric rise on jugular compression was normal, but the fall was slow.

On July 20, 1927 laminectomy of the third cervical to the first thoracic vertebrae was performed. A fusiform intradural swelling was immediately noted. After the dural opening was made, the swelling was observed to be a yellowish tumor fixed to, and lying on, the back of the cord. It measured 12 cm. in length and 3 cm. in breadth. A sagittal incision of this mass was cautiously made, and the impression was gained that the entire depth of the cord was involved. A V-shaped strip was longitudinally excised, and the incision was closed.

No change occurred during the short period of postoperative observation, during which time two roentgen ray treatments were given over the tumor. In a letter

13. Jaeger, F.: Ueber Lipome der hinteren Schliessungslinie, Zentralbl. f. Chir. **68**:2-6 (Jan. 4) 1941.

14. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: A Review of Fifty-One Cases, with an Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679-699 (April) 1931.

15. Adson, A. W.: Intraspinal Tumors: Surgical Consideration, Internat. Abstr. Surg. **67**:225-237 (Sept.) 1938.

received from the patient in October 1927 rapid improvement was reported. In 1942 we were informed[16] that since the letter of 1927 the patient had made a complete recovery and had become the sectional tennis champion, but that for six or seven years prior to 1942 his arms and legs had been becoming weaker.

The tissue removed consisted entirely of adult adipose tissue. Delicate fibrous septums divided the fatty mass. Blood vessels were sparse, and no nerve tissue, either cord or roots, appeared in the surgical specimen.

CASE 2.—An unmarried white woman aged 20 registered at the clinic on Jan. 30, 1935, complaining of pain in the back, numbness of the legs and weakness of the left leg. These symptoms had appeared after a recent injury.

The only item of importance in the medical and family history concerned the father, who had diabetes. The patient stated that she had been well in every respect until March 3, 1934, when she was struck in the abdomen by a cash register, which slipped from the hands of a fellow employee as it was being carried past her. The blow forced her back against the horizontal edge of a counter. A few hours later the back began to pain, and the next day pain appeared in the toes of the left foot. Two days later the pain ascended the left leg in a vague fashion, the toes of the left foot became numb and she tripped when she was climbing stairs. Both the pain in the leg and that in the back were made worse when she reclined and were ameliorated when she sat or walked. On March 10, 1934 girdle pain over an area, a handbreadth in width, developed about the abdomen. A week later a limp was noted. Ten days later the left thigh was involved in the numbness, previously limited to the toes. The next day the right ankle was painful, and a week later numbness became apparent in the right thigh. On April 8 a physician who had been consulted found analgesia below the waist. Sensation was almost entirely regained during the next eight weeks, and no progression was noted until September 1934, when the left leg was observed to be atrophic.

A lumbar puncture, performed on Oct. 16, 1934, revealed that the manometric readings were normal. The patient's blood pressure was noted to be elevated at about this time. During the first part of December the pain in the back had become much worse and had required administration of an unidentified medicament for relief. In January 1935 roentgenographic examination of the spinal column had led to a diagnosis of tumor of the spinal cord.

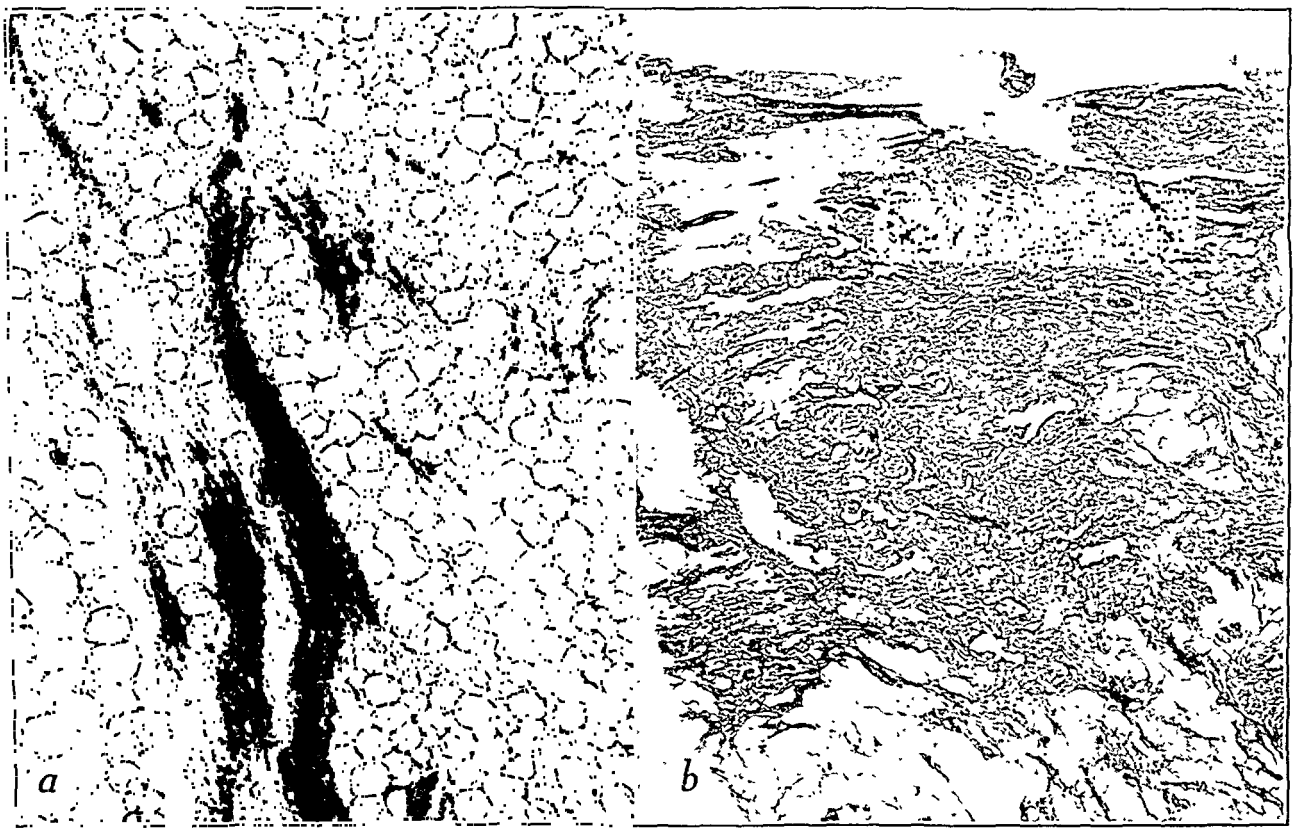

Fig. 1 (case 2).—(*a*) Fine bundles of root fibers traversing the lipoma (sudan III and hematoxylin; × 45). Note how intimately the root structure is infiltrated by the fat despite the absence of active-appearing tissue. (*b*) Fibrocellular tissue separating the fat from the cord. (Perdrau stain; × 20). Note the heavy extensions into the neural tissue at the top and how strands of neural tissue become sequestered (left center); also note the occurrence of islets of fat within this tissue.

Physical examination revealed nothing abnormal except in the nervous system. Sensation was normal above the ninth thoracic dermatome, but there were complicated sensory changes below this level. Appreciation of touch and temperature was absent over the right lower quadrant of the abdomen and the right thigh and was greatly diminished over the left side of the abdomen, *the left thigh and the lower part of the right leg and* foot. The lower part of the left leg and foot displayed minimal hypesthesia and hypalgesia. Vibratory and joint sensibilities were absent over the right ankle and were diminished over the left one. The entire left leg was moderately weakened, but the right leg was of normal strength. The hamstring reflexes were increased

16. Adelstein, L.: Personal communication.

on the left side, but the patellar and achilles reflexes, though moderately hyperactive, were of equal strength on the two sides. There were mild clonus of the left ankle and a Babinski sign bilaterally. The abdominal reflexes were absent.

Roentgenographic examination of the thorax revealed enlargement of the heart. Examination of the spine disclosed thinning of the pedicles of the fifth to the ninth thoracic vertebrae inclusive and erosion of the backs of the fifth to the eighth thoracic vertebrae. The spinal canal was much widened in this region. Lumbar puncture revealed an initial pressure of 10 cm. of fluid. This rose to 14 cm. after ten seconds of bilateral jugular compression and promptly fell back to the initial pressure on release. The Nonne test gave positive results, and the total protein content measured 120 mg. per hundred cubic centimeters of cerebrospinal fluid.

1943. She no longer uses crutches but is able to walk long distances with a cane. She is able to raise each foot off the ground to a distance of 12 inches (30 cm.), but is unable to jump at all. Clonus causes embarrassment if the foot is not properly supported. She is working in a self-supporting occupation.

The surgical specimen consisted of a longitudinal strip of the tumor, which included a small amount of the posterior columns of the cord on its anterior surface and permitted of accurate study of the relation of the tumor to the cord. The greater portion of the tumor was composed of typical adult adipose tissue. The free surface of the mass, the portion lying exposed on the posterior surface of the cord, was ensheathed by a fibrous capsule of moderate thickness, which in some places consisted of an outer layer, with the collagenous fibers running in a vertical direction, and an inner layer, with

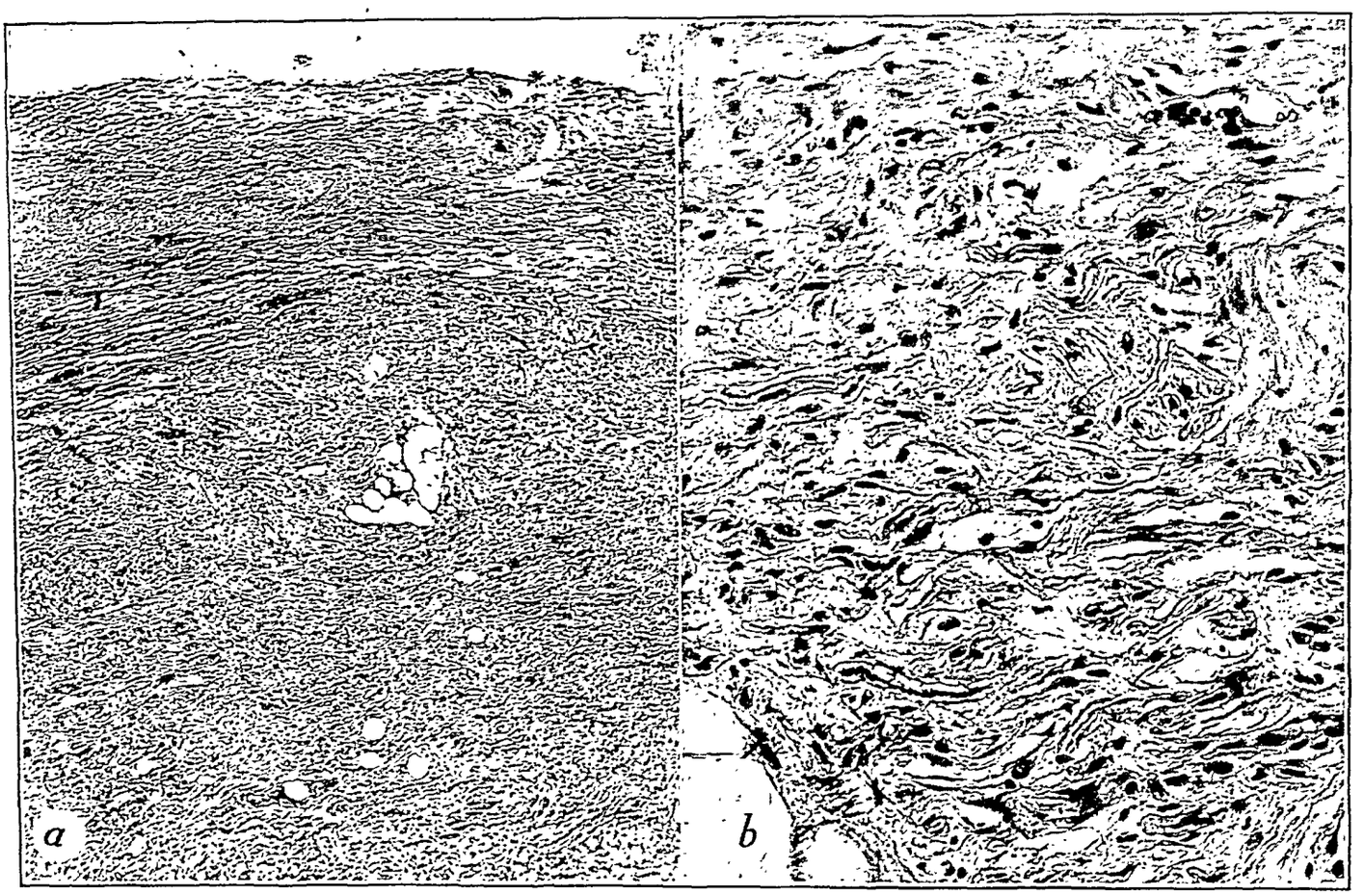

Fig. 2 (case 2).—Fibrocellular tissue separating the fat from the neural tissue. (*a*) The neural tissue at the top of the section is infiltrated by heavy strands, while the mass of tissue in the lower portion of the field shows scattered development of adipose tissue (hematoxylin and eosin stain; × 32). (*b*) Higher power of an area off the upper right corner of the islet of fat in the center of *a*. The Mallory-Heidenhain preparations of parts of this tissue showed roots contributing to the tangle (hematoxylin and eosin stain; × 215).

On Feb. 5, 1935 laminectomy of the fifth to the ninth thoracic vertebrae was performed. The bone was thin and excessively vascular. When the distended dura was opened, a large tumor on the posterior surface of the cord was exposed. This could not be separated from the cord, and a V-shaped longitudinal strip was taken from the most prominent meridian.

For three days the patient was paraplegic, but by the twentieth day she was able to stand and had control of her bladder. The right leg was analgesic, but the left leg showed only minimal hypalgesia. Vibratory sensibility was notably diminished on the right ankle but only moderately so on the left ankle.

By 1937 the patient was using crutches to get about and was able to take a few steps alone. A letter has been received describing her condition as of August

the fibers running in a horizontal direction around the tumor. The fibrocytic nuclei usually present in a capsule of this type were normally sparse. In some places numbers of small vessels were present immediately subjacent to the inner layer of this capsule, but on the whole the vascularity was not remarkable. The adipose tissue beneath the capsule did not contain any embryonic fat or active-appearing tissue.

As the interior of the tumor was approached from the capsular surface, one began to encounter small bundles of nerve fibers cut transversely, obliquely and longitudinally, all in the same section. These bundles had the undulating course and the connective tissue sheaths characteristic of peripheral nerves and must, therefore, be considered as rootlets traversing the tumor. The sections stained for fat showed beautifully these root-

lets coursing through a galaxy of red spherules (fig. 1*a*). The bundles of nerve fibers were mostly small and some of them contained only a few individual fibers. All the interstices were filled with fat, and the impression was gained that the fat had its origin from some structure originally lying within the root and bearing an intimate relation to its individual fibers. In other locations the rootlets lay in a moderately delicate stroma composed of anastomosing strands of fine collagenous fibers and cleftlike spaces, in which lay acidophilic granules in clumps. The only nuclei were pyknotic spindles, looking like the nuclei of fibrocytes, lying mostly in close association with the collagenous strands but sometimes seeming to be free in the clefts. The most adequate interpretation of this stroma is that it was myxomatous.

As the surface of attachment to the cord was approached, the amount of adipose tissue was diminished by heavy strands of cellular tissue extending into it. Finally, the fat gave way entirely to this cellular tissue, and a heavy, irregular layer of this tissue separated the adipose portion of the tumor from the neural substance of the cord. On the face of this separating layer next the cord one first saw sequestered islands of cord; then the cord tissue became prominent and was invaded by heavy strands passing into it (fig. 1*b*). This cellular tissue was composed of a tangled collagenous network bearing a variety of cells (fig. 2). Most of the cells were oval or spindle shaped, vesicular or pyknotic, and were certainly of connective tissue origin. Even in this tangle of fibers orientation was apparent. The course of the fibers was roughly parallel with the course of the nerve fibers in the white matter of the spinal cord.

No giant cells or mitotic figures were present in this tissue despite its superficial resemblance to sarcoma. No fat lay bare within or adjacent to the cord. The little fat within the cord was enclosed by the cellular connective tissue; in other words, fat was present in small amounts in the fibrous extensions from the septum into the cord. The Mallory-Heidenhain preparations revealed this cellular tissue to be of radicular origin. Lying between the dense, blue-stained collagenous fibers were faintly orange myelin tubules. The intraradicular connective tissue (endoneurium) had all but obliterated the nerve fibers, so strongly hyperplastic was it. The vascularity of this cellular connective tissue was minimal.

In certain sections in which the hyperplasia was less conspicuous and one was able to follow the roots to their entrance into the cord the roots were disrupted and distended with fat cells, so that the fat cells were partitioned one from another by septums bearing single layers of myelinated nerve fibers. Sections cut transversely across the tumor showed root fiber bundles and isolated individual myelinated nerve fibers closely applied to the cord in the septum separating the tumor from the cord; these roots were distributed over an unnaturally large portion of the circumference of the cord. Whereas posterior roots normally enter the cord along the posterolateral sulcus in a zone 1 or 2 mm. wide, in some locations the tumor roots were present in the septum over a segment of the circumference of the cord 1 cm. wide. Furthermore, these roots were cut transversely just as were the fibers of the cord.

CASE 3.—A man aged 41 registered at the clinic on Oct. 7, 1935, complaining of a burning sensation in the toes of the right foot and numbness, weakness and cramps of the right leg.

The patient's family history was noncontributory except that he had had a sister who had been obese before her death, of unknown cause, at the age of 50 years. The previous medical history is of interest. A pilonida cyst had been operated on in 1928. In 1930 the patien had a gastric hemorrhage. In 1932 he injured his bacl in a fall and was confined to bed for a month. He wa otherwise well, though obese, until March 1935, whei there appeared a burning pain in the toes of the righ foot and some acral numbness. During the next sever months this numbness gradually and unremittingly ascended the leg to the groin. A month after the onse of the burning the patient had noted weakness in th right leg, associated with twitching and cramping o the muscles of this leg.

The patient was obese, but the general physical examination did not reveal anything else significant. Positive findings elicited by the neurologic examination included moderate diminution of joint and vibratory sensibilities in the right leg and minimal diminution in th left leg, minimal hypalgesia and hypesthesia to th groin in the right leg, paresis of motion of the toes o the right foot, and, on the same side, increased patellai and achilles reflexes, a diminished hypogastric reflex, ar ankle clonus and a Babinski and related toe signs Lumbar puncture revealed colorless fluid and absence o block. However, the total protein amounted to 100 mg per hundred cubic centimeters of cerebrospinal fluid and the reaction for globulin was positive.

The patient was not seen again until February 1938 when he stated that the cramping had diminished but that the toes of the left foot had begun to burn during the previous November. The right leg tired greatly after he walked a few blocks, and a pain was present over the right lumbosacral area, which was made worse by his reclining on the right side and was relieved by his walking about. This pain was not exaggerated by coughing or sneezing.

Examination at this time showed progression of neurologic disturbance. The vibratory and joint senses were absent in the right leg and were moderately diminished in the left leg. There was hypalgesia over the left side of the sacrum, the posterior aspect of the left thigh and the left foot. Perception of pain in the right leg was normal. The entire right leg was moderately weakened and exhibited increased reflexes and clonus. The hypogastric reflex was almost absent on the right side, and there was a Babinski sign bilaterally.

Myelography, with radiopaque oil, performed on March 1, 1938, revealed partial obstruction to the descent of the cisternally injected oil at the lower part of the tenth thoracic vertebra. The lower end of the obstructing mass lay in the middle of the eleventh thoracic vertebra. Erosion of the pedicles of the eleventh vertebra was noted in these myelograms.

Laminectomy of the tenth and eleventh thoracic vertebrae, performed on March 4, 1938, revealed a yellow intradural tumor lying on the right posterior aspect of the spinal cord, intimately attached to several root filaments at their emergence from the cord and possibly involving the cord itself. The incision was widened to the right to effect removal of this tumor, and another tumor, extradural in location, was encountered on the ninth thoracic root. The second tumor was entirely separate from the larger, intradural tumor and did not occur on the same root, lying, as it did, on the root above. Both tumors were removed under the impression that they were neurofibromas. The cord was compressed by the intradural tumor to about one-third normal size.

On the seventeenth postoperative day there was still weakness in the right leg. The Babinski sign was not present on the left side, but ankle clonus, stronger on the right side than on the left, was elicited. Joint an-

vibratory senses had returned to normal. There was absence of appreciation of touch, pain and temperature over the right lower quadrant of the abdomen and the front of the right thigh. On the patient's return to the clinic, on Aug. 25, 1938, he stated that he had been getting about with a cane until three weeks prior to this date, when he was caused to fall by his right leg's jerking involuntarily into flexion. The legs tired more easily and felt stiffer after this episode than they had before. Cramping began in the right calf. The left leg would involuntarily flex when the patient was in bed. Perineal numbness was noted at stool. Examination showed considerable weakness of the hamstring muscles and the muscles of the calf, moderate weakness of the quadriceps and minimal weakness of the psoas and gluteal muscles, all on the right side. The left leg was strong. Both legs exhibited increased tone. Ankle clonus and increased tendon reflexes were present on the right side. A Babinski sign was elicited on each side. Joint and vibratory senses were absent in both legs to the knees. Cutaneous sensibility was diminished below the tenth thoracic dermatome and was absent below the knees. Roentgenographic examination showed only absence of the laminas which had been removed. A lumbar puncture yielded colorless fluid, containing 55 mg. of protein per hundred cubic centimeters. There was no block. Further surgical treatment was not advised. The patient has not responded to our recent inquiry, and his present status is unknown.

The intradural tumor consisted of adult adipose tissue, traversed by heavy fibrous septums bearing bundles of root fibers. At the extremity of some of these fibrous septums there was present glial tissue similar to that in the white matter of the spinal cord. In some regions the rootlets to this glial segment were considerably disorganized and lay in the fibrous stroma in small bundles separated by heavy collagenous bands and small groups of fat cells. In another septum a single large root was almost the sole occupant. In one location this root became a tangled mass of hyperplastic endoneurium, which merged imperceptibly with the surrounding heavier collagen strands at the periphery and was not separated from the surrounding tissue by a condensed band of connective tissue. Small amounts of fat lay within the fibrous septums, but no fat was present within the hyperplastic root. Almost all the fat lay in the lobules between the root-bearing septums. The vessels of this tumor were scanty. Tissue from the extradural tumor is no longer available.

CASE 4.—The patient presented himself at the clinic in September 1943, complaining of pains in the back, the thorax and the right leg. He was 22 years of age, single and a farmer.

The family history was without significance. The patient had been well until four years prior to his coming to the clinic, when he became jaundiced for two weeks and was put to bed. The first day out of bed, after the jaundice subsided, he carried a quantity of lumber from the basement and the following day had a sore back, which caused him to walk bent over. Shortly after this the right leg felt stiff and seemed to drag. A certain degree of recovery occurred, but during the year prior to registration at the clinic the patient was bothered by bouts of pain in the right leg, which lasted about two hours and were followed by weakness in the leg. In August 1943 soreness reappeared in the upper part of the back, and the pain seemed to run into the left side of the thorax. There was a spot in the midthoracic segment of the spinal column which pained on walking. Coughing and sneezing caused pain in the midthoracic region of the back and around the lower part of the sternum. A pain appeared in the right thigh whenever the patient exercised. His temperature had been 100 F. since August.

The patient was well built and seemingly well; he appeared moody and was perhaps less bothered by his pains than he asserted. The general physical examination revealed nothing of significance except for a low grade fever. The neurologic examination revealed only that the left pupil was larger than the right, and the vibratory and joint sensibilities were diminished in the lower extremities.

Routine examination of the blood, flocculation tests and urinalysis gave normal results. Roentgenograms of the spinal column showed erosion of the inner margins of the pedicles of the second and third thoracic vertebrae, particularly of the right pedicle of the third vertebra. Spinal puncture was performed on September 18. The initial pressure was 15 cm. of fluid. On jugular compression the pressure rose to 19 cm. of fluid. The fall was slow. Ten cubic centimeters of the colorless fluid was removed, and the final pressure was 1 cm. The fluid contained 11 cells per cubic millimeter, small amounts of globulin and 120 mg. of total protein per hundred cubic centimeters.

Myelography, with the use of radiopaque oil, was performed on September 22. There was almost complete obstruction to the passage of the oil upward at the fourth thoracic interspace. This deformity was mostly on the right side and was interpreted as being due to an intradural extramedullary tumor. Later the same day laminectomy of the fifth thoracic to the seventh cervical vertebrae was performed. The distal end of the tumor lay in the lower end of the incision; but the upper pole was beyond the highest exposed segment, and the surgeon deemed it unwise to go farther, since the growth could not be separated from the cord. The tumor was yellow and had the appearance of adult fat. A small fragment was removed from the dorsal surface, and this proved to be adult adipose tissue with increased stroma.

The patient's convalescence was complicated by postoperative hematoma. After the removal of this clot gradual recovery occurred.

Clinical Features of Intradural Lipomas.—Twenty-nine cases of intradural lipoma are available for comparison and analysis. The distribution of these tumors between the sexes appears to be about equal. Fourteen patients were females; 12 were males, and the sex of 3 patients was unknown. This slight inequality at least does not run counter to the distribution between the sexes of lipomas in other locations which is given as about 3:2 in favor of females (Geschickter[17]).

Consideration of the ages at which the first symptoms began leaves one with the impression that this tumor makes its presence known only during three rather well delimited age periods: before the age of 2 or 3 years, on the patient's reaching manhood or womanhood and in early middle age. In only 4 cases did the tumor fail

17. Geschickter, C. F.: Lipoid Tumors, Am. J. Cancer **21**:617-641 (July) 1934.

to conform to this generalization. The distributions of the ages of onset are charted in figure 3. In view of what has been said by other authors and what we shall have to say regarding the probable existence of most of these tumors from before birth, it might be held that the age of onset is of little importance. On the other hand, it seems to us that the onset of symptoms due to intradural lipoma must be capable of some rational explanation having to do with increased deposition of fat at certain times of life, interference with the blood supply to the spinal cord at a time when the vascular system begins to be less adaptable than before, edema from trauma, and perhaps other factors.

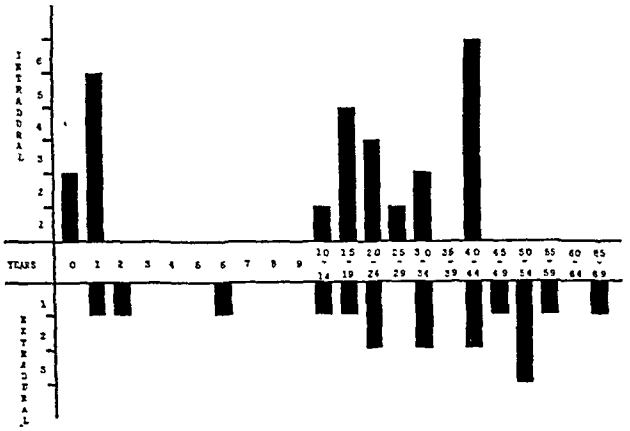

Fig. 3.—Ages at clinical onset of intraspinal lipomas. The values for the intradural lipomas are plotted above and those for the extradural lipomas are plotted below the axis of the abscissas.

Among the cases in which trouble was experienced during the early years of life there were 3 of early death. The tumors in these 3 cases were the largest in the entire series, 2 of them extending throughout the length of the cord, and other severe defects were associated. In each of the 4 instances of early onset without early fatal termination the duration before operative intervention or death was long, being four, ten, thirteen and fifteen years, as though the trouble was due to a slowly augmenting pressure by a soft mass without infarction of the spinal cord. The tumors manifesting themselves very early, accordingly, seem accounted for on the basis of more or less massive development of a fatty mass within the dura at some time in embryonic life. In the one group this mass is very large, and other severe defects help to express the faultiness of the germ plasm or the seriousness of the factor operating in utero on the embryo and rather overshadow the intraspinal tumor with regard to the clinical picture and as a cause of death. In the other group the fatty mass is less large but so nearly fills the neural canal that it is not long in reaching such a size as to interfere with function of the spinal cord. The long history of trouble is to be considered an expression of the slow growth of the tumor and the ability of the spinal canal to accommodate it by widening. A variety of less severe developmental defects may accompany the intraspinal lesion.

The clustering of cases around the beginning of the third decade may have something to do with the filling out of the body generally, through the deposition of fat in the adipose tissue. The fact that 6 of the 7 patients in this category were females does not detract from this hypothesis. If such deposition is the correct explanation, then it is probably dependent on a nidus present before birth, as indicated previously.

The grouping of the cases in the early part of the fifth decade might be suspected to result from the final overtaking by a slowly increasing mass of a cord the vessels of which are becoming increasingly sclerotic and less and less adaptable to outside interference.

In only 1 of the cases (Ritter[18]) was the histologic picture significantly different from that of numerous other tumors of this type. In this single case there was definite evidence of new formation of fat and real activity, so that the sudden onset must be largely attributed to rapid increase in size of the tumor.

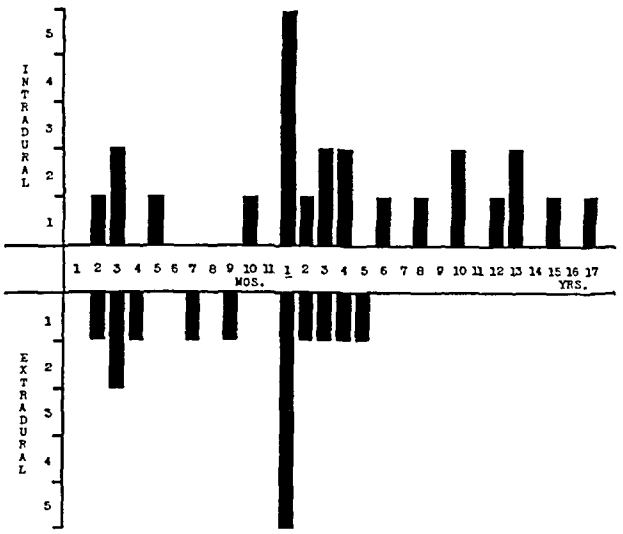

Fig. 4.—Duration of symptoms arising from intraspinal lipoma before death of the patient or surgical removal of the tumor. The values for the intradural lipomas are plotted above and those for the extradural lipomas are plotted below the axis abscissas.

Reflections on the duration of symptoms before the death of the patient or before surgical removal are rather unproductive because the terminal issues are not equivalent. Figure 4, dis-

18. Ritter, A.: Ein Lipom der Meningen des Cervicalmarks, Deutsche Ztschr. f. Chir. **152**:189-209, 1920.

playing the duration of symptoms until operation or death, is worth a moment's attention. It shows the great variation, but also indicates how in many cases, contrary to the general impression, the lipoma is of short duration. The median period is somewhere between three and four years.

The symptoms of the intradural lipomas are perhaps a little different from the symptoms of tumors of the spinal cord as a whole. Spontaneous pain, aside from painful cramp, was a prominent symptom in 10 of the 29 cases. In 3 cases (Oppenheim and Borchardt[19]; case 1 of this series; Bucy and Gustafson[20]) pain was limited to the spine. In 3 cases there was distal pain which must have been due to the tumor but was not explicable on the basis of root irritation or osseous involvement. In only 4 cases were there pains which probably were of root origin. It is clear that definite root pain is not often caused by an intradural lipoma, despite the frequent involvement of roots by the tumor. The explanation depends on the fact that this tumor is almost always so firmly fixed to the cord that the traversing roots are not pulled on when the intraspinal hydrodynamic relations suddenly shift.

An early symptom in 4 cases was awkwardness in use of the arms or legs not associated with manifest weakness. In Stookey's[21] and Bucy and Gustafson's[20] cases walking was retarded and was never normal. In the latter case the patient became unskilful in use of the hands. In case 1 of this series a maladroit gait, and then clumsiness of the arms, developed. In Jabotinski's[22] case awkwardness of the left arm was observed at the onset of the trouble.

Other symptoms were those common to all intraspinal tumors and were of no diagnostic help. Nine of the 29 cases of intradural lipoma were of no value in determining which features of the clinical examination were characteristic, if any. Many of the remaining cases are not of great value for a variety of reasons.

In 8 cases (Turner[23]; Oppenheim and Borchardt[19]; Ritter[18]; Elsberg's case VI[24]; Scherer[25]; Guillain, Bertrand and Salles[26]; cases 1 and 2 of this series) there were displayed what were essentially transverse lesions of the cord without specificity of selection of fiber tracts.

In case 3 of this series, that of a tumor of the right posterolateral region of the cord, the symptoms were about what one would expect. Appreciation of pain was diminished in the sacral dermatomes of the opposite side. Joint and vibratory appreciation was affected bilaterally, but more on the side of the tumor than on the opposite side. Abnormal reflexes were present in both legs, but only the right leg was weakened. The absence of sensory change in the dermatome served by the affected segment and root of the cord is explained by the slight linear extent of the portion of the cord affected and by overlap from adjacent dermatomes.

Before lumbar puncture Elsberg's[24] patient (case 8) had only spastic paraplegia, which was worse on the side on which the tumor lay than on the other side. After the puncture total anesthesia developed up to the fourth thoracic dermatome. The patient of Bucy and Gustafson[20] was tetraparetic, hypesthetic below the clavicles, insensitive to joint motion and vibration in the legs and hyposensitive in the arms to these modalities, but he had no disturbance of appreciation of pain or temperature. The most severe disturbance, the loss of joint and vibratory sense, was in accord with the position of the tumor on the posterior surface of the cord. Fay's[27] patient had spastic paraparesis and impaired vibratory and position sense in the legs until a lumbar puncture was done. Then the vibratory and position defect increased, and the appreciation of pain and temperature became impaired below the sixth thoracic segment, a dissociation the reverse of that displayed by Bucy and Gustafson's patient. Stookey's[21] patient had spastic paralysis of the

19. Oppenheim, H., and Borchardt, M.: Weiterer Beitrag zur Erkennung und Behandlung der Rückenmarksgeschwülste, Deutsche Ztschr. f. Nervenh. **60**: 1-31, 1918.

20. Bucy, P. C., and Gustafson, W. A.: Intradural Lipoma of the Spinal Cord, Zentralbl. f. Neurochir. **3**: 341-348 (Jan.) 1939.

21. Stookey, B.: Intradural Spinal Lipoma: Report of a Case and Symptoms for Ten Years in a Child Aged Eleven; Review of the Literature, Arch. Neurol. & Psychiat. **18**:16-43 (July) 1927.

22. Jabotinski, J.: Fibrolipome intradural de la moelle, Rev. neurol. **72**:15-31 (July) 1939.

23. Turner, F. C.: Lipomatous Tumor (? Sarcoma) of the Spinal Cord, Tr. Path. Soc. London **39**:25-27, 1888.

24. Elsberg, C. A.: Tumors of the Spinal Cord and the Symptoms of Irritation and Compression of the Spinal Cord and Nerve Roots: Pathology, Symptomatology, Diagnosis and Treatment, New York, Paul B. Hoeber, 1925.

25. Scherer, E.: Die extramedullären pialen Lipome an der hinteren Wurzellinie des Rückenmarks (Kasuistischer Beitrag), Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:507-520, 1936.

26. Guillain, G.; Bertrand, I., and Salles, P.: Les lipomes spinaux intra-duraux, Ann. de méd. **42**:119-131 (June) 1937.

27. Fay, T.: Vasomotor and Pilomotor Manifestations: Their Localizing Value in Tumors and Lesions of the Spinal Cord; a Report of Thirteen Verified Cases, Arch. Neurol. & Psychiat. **19**:31-46 (Jan.) 1928.

legs, flaccid paralysis of the arms, absence of vibratory appreciation in the legs and disturbance of pain and touch appreciation from the fourth dermatome on the left side only.

Braubach's [28] patient was too young and too sick for satisfactory sensory examination, but she had hypesthesia and hypalgesia in the arms and legs and paralysis of the right arm and of both legs. It is remarkable, and of some significance, that the right arm was palsied while the left remained unaffected. The large tumor involved the segments of the cord giving rise to the brachial plexus and lay on the same side as the paralyzed arm. While the roots lay anterior to the tumor, the unilateral palsy is best explained on the basis of destruction of the roots by stretching (?), rather than of compression of the anterior horn, and the paralysis must have been of the lower motor neuron type. Scherer's [25] patient had a palsied arm from a tumor in a similar location, but in this instance the mass enclosed many roots. The same speculations apply to Scherer's case as to Braubach's; and if these 2 instance of paralysis of the homolateral arm may be explained as has been suggested, this feature is unique to lipoma. No other single tumor possesses sufficient linear extent to implicate enough roots to cause paralysis of the arm as a whole. Other tumors may of course be of considerable linear extent, but the paralysis is bilateral because it is due to compression or destruction of the anterior horn and both sides are affected.

Painful flexion of the neck and tenderness of the spinal column were observed in a few cases, but these features in no wise help to distinguish lipoma from other intraspinal tumors. Anisocoria was present in a few cases of cervical tumor, and in the 1 case in which the relations of the tumor were accurately established (Jabotinski [22]) the tumor lay on the side of the miotic pupil, as is to be expected.

Spinal puncture was performed in 13 of the 29 cases of intradural lipoma. In 5 cases the report failed to mention the results of the manometric study. In 3 of the 8 remaining cases there was no hydrodynamic block; in 4 cases there was partial block, and in 1 case, almost complete block. The cerebrospinal fluid was abnormal in each case in which block was absent. In 1 case only the reaction for globulin was positive; in the second case the total protein amounted to 100 mg. per hundred cubic centimeters of fluid, and in the third case the fluid was xanthochromic and contained increased protein. In this case the initial pressure was zero, but jugular compression caused a prompt rise to 10 cm. of fluid. Release of the compression was followed by a prompt return to zero. Significantly, this manipulation caused pain to appear in the thorax —pain such as was one of the patient's presenting symptoms. In 1 of the 4 cases in which there was partial block the fluid was normal. In this case the evidence of block was a rapid, but steppage, type of fall of fluid pressure. In 2 cases in which there was partial block the total protein amounted to 120 mg. per hundred cubic centimeters of fluid. In the fourth case the fluid was xanthochromic and globulin was present, but the total protein content was not reported. In the case of complete block the fluid was yellow and contained large amounts of globulin. In 2 of the 5 cases in which no manometric data were reported the cerebrospinal fluid was yellow and contained globulin; in 1 case it contained globulin; in 1 case it was diagnostic of tumor of the spinal cord, in an unspecified manner, and in 1 case it was reported to contain 220 mg. of total protein per hundred cubic centimeters.

The series is too small to enable one to relate the size of the tumor to the degree of block. The noteworthy circumstance is the failure of total block in at least 4 instances (Bucy and Gustafson's [20] case; cases 1, 2 and 4 of this series), in which the tumors were of such size as literally to dwarf the usual extramedullary block-producing tumor. The lipomas are somewhat similar to true intramedullary tumors in their effects on the pathway of the spinal fluid. They produce a fusiform enlargement of the cord and expand ever so slowly. They do not kink the spinal cord by pressing on it at one spot or completely fill the subarachnoid space in one small region; rather, they run to considerable length and leave the pathway stenosed but open. The presence of normal fluid in but 1 of 13 cases, and this in the case of a very small tumor which altered the hydrodynamic relations of the spinal fluid, attests the tendency to discoverable encroachment, if not obstruction.

Roentgenograms or myelograms or both were made in 14 of the 29 cases. In 5 instances localized widening of the spinal canal by erosion of the vertebral body or pedicles was noted; in 1 instance the interpretation was kyphosis and arthritis; in 4 instances the spinal column was normal, and in 4 instances the report of the myelogram did not include mention of the bony changes, if any. The tumors associated with bony changes were not significantly larger than the tumors associated with a spinal column which was reported as normal. Indeed, one of the small-

28. Braubach, M.: Ein Fall von Lipombildung der Rückenmarkshäute, Arch. f. Psychiat. **15**:489-495, 1884.

est tumors of the series (case 3 of this series) caused erosion of one pedicle. Neither did the age of onset or the duration of symptoms seem to bear any relation to the presence of bony changes. In Stookey's [21] case, however, in which there was the most extraordinary widening of the canal, the onset of the trouble appeared at a very early age. It is probable that if more roentgenographic studies were reported a case could be made out for the more constant appearance of bony changes with the early onset and long duration of symptoms. In 8 cases myelographic studies were made. In 3 cases there was complete or almost complete obstruction; in 2 cases, partial obstruction, and in 1 case, indication of tumor of an unspecified nature; in 1 case the results were unknown, and in 1 case (Eckart [29]) there was no evidence of any obstruction, although the tumor was of great linear extent.

Other physical defects were rather commonly associated with the lipomas. Extreme instances of such an association are the cases of Wolbach and Millet,[7] of Baker and Adams [30] and of Bielschowsky and Valentin,[31] in which the defects were too numerous and too obscurely related for one to say much except to classify the lesions as "multiple congenital anomalies." In 2 cases subcutaneous lipomas overlay the deeper lipoma, an occurrence which is immediately arresting, seeming to exceed in importance its mere application to the matter at hand to bear on the question of the derivation of the leptomeninges. It is probably of little significance that in 2 cases the patients were obese. The occurrence of pilonidal cysts in 2 cases should not cause one to interpret the lipoma in a similar embryokinetic light.

The distribution of the intradural lipomas along the length of the spinal cord is subject to some law which favors certain regions and tends to avoid others. In analysis of data on the tumors from this standpoint, we took care to translate the various data into terms of the actual level of the cord by referring to figure 54 of the 1939 edition of Ranson's [32] textbook. Although errors are unavoidable in an attempt to decide on which segments of the cord were exposed from descriptions of laminectomy incisions, the deviation is not likely to be large, and considerably more accuracy is attained than if laminectomy levels and segment levels of the cord were mingled in the making of comparisons. In 12 cases the tumor lay entirely above the seventh thoracic segment of the cord, and in 7 cases, entirely below the sixth thoracic segment; in 3 cases the tumor was small and occupied exactly the midthoracic region; in 5 cases the tumor was very long and lay both above and below the midthoracic level; in 1 case it was shorter, and in 1 case the location was not given. The only tumors involving the upper sacral segments were the 3 huge ones appearing as a feature of multiple congenital anomalies and attended by early death —not to say that the lesion of the cord was the cause of death—and the tumor reported by André-Thomas and Jumentié.[33] The most accurate manner of dealing with the problem of segmental distribution is to show graphically the

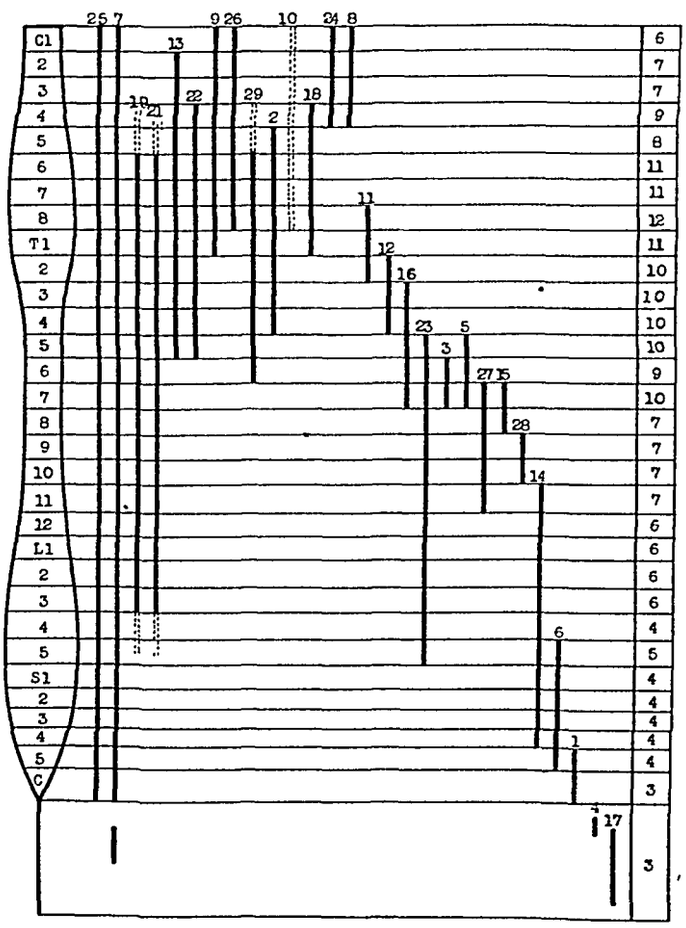

Fig. 5.—Longitudinal distribution of intradural lipomas with reference to the spinal cord. Data concerned with laminectomy and the like obtained from reports in the literature have been translated into terms of the actual segment of the cord probably involved. Pure surmises are indicated by dots. The column to the right indicates the total number of times each segment was involved by tumor. The number at the top of each tumor refers to the number of the case as listed in table 1.

29. Eckart, G., cited by Bucy and Gustafson.[20]

30. Baker, A. B., and Adams, J. M.: Lipomatosis of the Central Nervous System, Am. J. Cancer **34**:214-219 (Oct.) 1938.

31. Bielschowsky, M., and Valentin, B.: Ueber ein Lipom am Rückenmark mit Hydrosyringomyelie und anderen Missbildungen, J. f. Psychol. u. Neurol. **34**: 225-233 (Feb.) 1927.

32. Ranson, S. W.: The Anatomy of the Nervous System from the Standpoint of Development and Function, ed. 6, Philadelphia, W. B. Saunders Company, 1939.

33. André-Thomas and Jumentié, J.: Lipome du cône terminal, Rev. neurol. **20**:222 (Jan. 25) 1912.

number of times each segment of the cord is occupied by tumor (fig. 5). The lower cervical and upper thoracic region is the favorite seat of these tumors, and the conus medullaris is the most avoided region.

The distribution of the tumors around the circumference of the cord shows a predilection for certain segments of the circle and an avoidance of others. The study of this feature is attended by considerable inaccuracy, for detailed descriptions of the circumferential extent of the tumors are scarce and one must often depend on inference. Operative cases are of less value in the determination of this point than necropsy cases. Despite these reservations, the plotting of this relation to the cord brings out certain striking facts (fig. 6). In 21 cases the tumor involved the dorsal aspect of the cord between the dorsal root lines. In 6 cases the tumor was entirely anterior to the root lines or involved

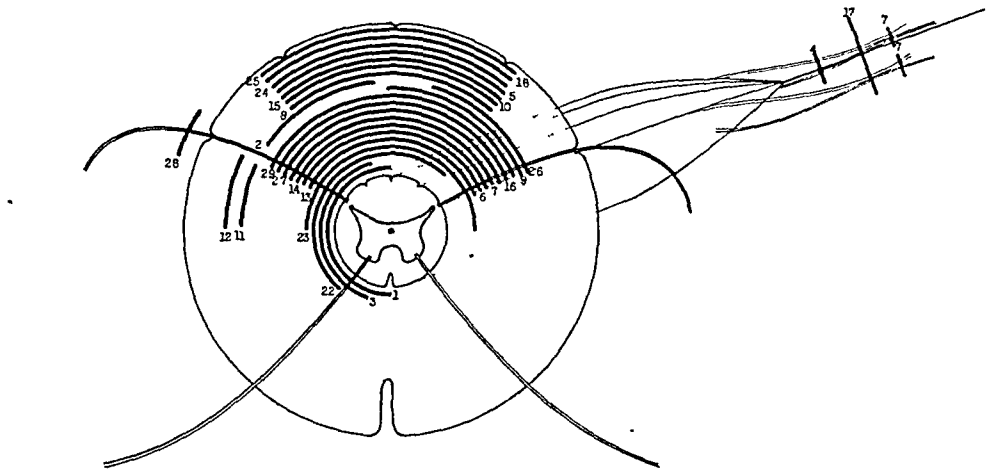

Fig. 6.—Circumferential distribution of the intradural lipomas with reference to the spinal cord. The space between the small circular structure representing the cord and the larger circular structure of similar outline represents the pia, and it is in this space that the tumors lie. The extremity of the cord lying off to the right represents the cauda equina. The numbers refer to cases as enumerated in table 1.

the roots themselves. In the cases of Gowers [9] and Turner [23] the tumor involved, in addition to the dorsal surface, the lateral portion of the cord. In Elsberg's [24] 2 cases the tumors differed from the other lipomas in that they originated just anterior to the dorsal roots and were not traversed by them. In 8 cases the tumor appeared to have arisen from the dorsal surface of the cord without incorporating roots in its substance. The state of involvement of the roots was unknown in 6 instances. In 15 of 26 cases the tumor implicated roots, and in 1 or 2 cases it probably did so; in 5 cases the tumor definitely did not involve the roots, and in 3 others it probably did not. Scherer [25] expressed the opinion that the tumor reported by him actually arose in the line of the posterior roots. Case 3 of this series is unique because of the origin of the tumor from a thoracic dorsal root alone. In the case reported by Beykirch [34] the tumor arose from the cauda equina. The tumor of the filum in the case reported by Spiller,[6] which enclosed root fibers, and the smaller tumors in Wolbach and Millet's [7] case bring to 4 the cases of tumors arising in locations other than the medullary pia.

Recapitulation.—Certain symptomatic, clinical, laboratory and gross anatomic features of the intradural lipoma are at variance with the corresponding features of tumors of the spinal cord as a whole, and it is possible that attention to these features in the future may make possible the diagnosis of the tumor prior to exposure. Tumors making themselves known before the third year of life, about the beginning of the third decade and about the beginning of the fifth decade of life are suspect. The duration of the symptoms is of little help, but if the history is long lipoma should be especially considered. Pain of various sorts is common in cases of lipoma, but if the pain is definitely radicular, especially if limited to a narrow zone, the presence of lipoma is unlikely, though not impossible. Awkwardness in the use of the hands and ataxia in walking when recited as early symptoms and before weakness was noted suggest lipoma, especially if the patient is young.

Physical findings are of little help. Signs suggesting lipoma are diminution of joint and vibratory sensibility out of proportion to other sensory changes and unilateral flaccid paralysis of an extremity due to an intraspinal tumor. If a lipoma is present, one is not likely to discover a complete manometric block at the time of lumbar puncture, but the fluid will almost certainly contain globulin or excessive protein (frequently

34. Beykirch, A.: Klinischer Beitrag zur Buerteilung der myelographischen Röntgenbilder, Beitr. z. klin. Chir. **142**:301-321, 1928.

only small excesses) or be xanthochromic. Roentgenograms cannot be counted on to reveal bony changes, but if there are evidences of widening of the spinal canal over three, four, five or more vertebrae the presence of a lipoma is suggested. The myelogram cannot be counted on to enable one to diagnose the exact relation of the tumor to the cord. If, in the presence of the suggestive features mentioned, the examination points to a cervicothoracic location for the trouble, the possibility of lipoma is good. The presence of congenital defects, especially a lipoma of the back overlying the suspected segments of the cord, lends confidence to the diagnosis.

Pathologic Features of Intradural Lipomas.—Certain aspects of the pathologic picture of intradural lipoma have been briefly mentioned to point up the discussion of the clinical changes, but a more minute inquiry is now in order. Characteristics which bear looking into are the relation of the fatty mass to the neural tissue and its envelopes, the reactions evoked in the neural tissues and its envelopes, the amount and origin of the stroma and capsule of the tumor, the amount of involvement of roots and the nature of this involvement and the type of fat composing the tumor.

Concerning the exact relation of these tumors to the cord there is little disagreement. After 11 cases are excluded because of lack of sufficient information or because the tumor lay on the roots or the filum terminale, there remain 18 cases which are of importance with respect to the relation to the cord, and in all these cases, with 1 possible exception, the tumor lay on the side of the cord in an extramedullary position but so firmly and intimately attached to the cord that the superficial resemblance was to intramedullary tumor. In every case there was described a layer of connective tissue which separated the adipose tissue from the neural tissue, and in 11 cases (Gowers; Braubach; Ritter; Elsberg [24]; Bielschowsky and Valentin; Fay; Scherer [25]; Guillain, Bertrand and Salles; Bucy and Gustafson; case 2 of this series) the authors stated the opinion that the tumor arose in the pia and that the lamina between the cord and the tumor was of pial origin.

Cases likely to be the subject of controversy over this matter of pial origin and extramedullary location are those of Elsberg,[24] Turner,[23] Jabotinski [22] and Sachs and Fincher.[8] Elsberg described the location of his 2 tumors as "subpial," but that he did not mean by this that they were intramedullary is shown by his classifying them with the extramedullary tumors. Turner's tumor, described as invasive, and probably malignant, presented on the surface, and the fatty portion was separated from the cord by a mass of fibrous tissue which had undergone proliferation.

The tumor described by Jabotinski is the most controversial because the ends of it lay within the medullary substance. A case can be made out for the origin of this tumor within the cord and its secondary migration to a superficial location except for the poles. This mechanism was suggested by Stookey.[21] Contrary to Stookey's statement, however, these tumors show a capsule separating the fat from the cord, but this capsule is not often of such a nature that the tumor can be lifted from it, as in the case of Sachs and Fincher. In Jabotinski's case the presence of roots within the tumor speaks for some origin other than intramedullary, with subsequent migration. To reconcile this tumor with the hypothesis of pial origin it is necessary to suppose that the hyperplastic pial septum invaded the cord at the poles of the tumor and then became filled with fat.

The tumor described by Sachs and Fincher was reported as intramedullary, but attention to the excellent illustrations and the relations described in the operative note leave no doubt that the tumor was separated from the cord by an inner layer of pia and that the only dispute is one of terminology.

Another point of importance is that fat has never been described as lying bare within the neural tissue or with only the sparse stroma that one might reasonably associate with formation of lipoma. Rather, the only fat lying within the cord is associated with the heavy extensions running into the cord from the hyperplastic septum. Jabotinski's case is a possible exception.

The glial and neural elements of the cord respond to the presence of the tumor by degenerating when the pressure or interference with the blood supply becomes critical. In all other instances the cord seems to tolerate the fatty parasite well. The same cannot be said for the connective tissue of the leptomeninges, the pial extensions into the cord or the endoneurium of the roots. Twenty-one cases are pertinent to this phase of the study, in which either necropsy or operation was done and enough tissue was removed to show the nature of the changes.

In 8 of the 21 cases the tumor showed little or no reaction of connective tissue. The tumor in Elsberg's [24] case VI was described as a fibrolipoma, but no mention was made of pial or root hyperplasia and the tumor was removable. Beykirch [34] observed only a fine stroma with few nuclei in his tumor of the cauda equina, but the whole tumor was not removed. The tumor re-

moved by Sachs and Fincher is one of which one may be certain, since it was removed *in toto,* was shelled from the cord and was histologically negative for evidence of hyperplasia of the connective tissue. The tumor described by Bucy and Gustafson had only increased reticulin near its attachment to the cord and a heavy capsule on the free surfaces. Elsberg's description of the tumor in his case VIII was accompanied by photomicrographs demonstrating much more cellularity in one location than in the other, but there was nothing in the description to indicate pial or root hyperplasia. In the cases of Wolbach and Millet [7] and Fay [27] there was minimal "invasion," and though this probably meant invasion by hyperplastic pial extensions, it is safest not to make the assumption. The tumor of the filum described by Spiller [6] is the last of the 8 tumors.

In 13 cases (Gowers [9]; Braubach [28]; Turner [23]; Oppenheim and Borchardt [19]; Ritter [18]; Henneberg [35]; Bielschowsky and Valentin [31]; Scherer [25]; Guillain, Bertrand and Salles [26]; Baker and Adams [30]; Jabotinski [22]; cases 2 and 3 of this series) the extent of changes in the connective tissue ranged from moderate to remarkable. The alterations were by no means similar in all cases. On the one hand are the case of Gowers,[9] in which slight pial thickening and abundant fibrous tissue appeared in the portion of the tumor next the cord, and the case of Bielschowsky and Valentin,[31] in which pial thickening and radicular endoneural proliferation were present; on the other hand are the cases of Scherer [25] and of Guillain, Bertrand and Salles [26] and case 2 of this series, in which there was conspicuous proliferation of the endoneurium of traversing roots. It is probable that in Stookey's [21] case and in cases 1 and 4 of this series the tumors would show a similar picture if they were examined *in toto.* One-half the tumor in Turner's case was fibrous and cellular to such a degree that it was considered sarcomatous. In Ritter's case the tumor contained cellular strands running into the cord and many embryonic fat cells and was considered to be a lipoblastoma.

The question arises whether these proliferative changes were actually induced in the connective tissue by the fat, or whether they constituted the primary defect and the deposition of fat was secondary. This of course is difficult to answer, but it is likely that in some cases merely a pial thickening was secondary to presence of the fat (as would be the adhesion of the dura to the tumor, reported in a few cases), while in other cases both the fat and the proliferation of connective tissue were manifestations of the same process.

The septal and stromal elements of the tumor have connections with the capsule and must be of similar pial origin. A false impression of the amount and nature of the connective tissue present may be obtained if too much attention is paid to the piece of fat removed from the surface of a lesion incapable of being totally removed. Most of the tumors showing pronounced fibrous hyperplasia at the tumor-cord interface are almost wholly fatty in the locations from which one would take a bit for biopsy.

In 15 cases nerve roots traversed the lipoma; in 5 cases they did not, and in 2 cases roots were probably implicated but surgical exploration was not extended to determine this point. In 8 instances (Gowers [9]; Spiller [6]; Ritter [18]; Scherer [25]; Guillain, Bertrand and Salles [26]; Baker and Adams [30]; cases 2 and 3 of this series) the roots were more or less extensively broken up by fat, which in some manner had insinuated itself into the spaces between the individual nerve fibers. Instead of the root fibers traversing the fat in well defined bundles of normal size, the bundles were filled with fat, as though the fat had arisen from an element in intimate contact with the individual fibers or had extensively invaded from without. The appearance of such an area on cross section, especially with the myelin stains, is somewhat like that of the magnetic field of a straight bar magnet when delineated by iron filings on a sheet of paper. Scherer's [25] figure 3 is the most perfect illustration of this iron filing effect imaginable, for it shows the complete pattern. Figure 4 in the article by Guillain, Bertrand and Salles [26] and an illustration in Spiller's report [6] show this effect less completely. Figure 1 *a* of this study represents a small area of a root-bearing field cut on a plane parallel with the fibers, but the field is too small and the magnification too great to demonstrate the iron filing effect.

The fatty tissue of the intradural lipoma is practically never any but adult adipose tissue. In 20 reports the fat was described by this term or by synonymous terms. In an additional 5 cases the tumor was a mixture of adult adipose tissue and fibrous tissue—fibrolipoma. In the case of Ritter [18] all the transitions from embryonic fat to adult fat were shown. Along the capsule and septums this new formation of fat was going on. This lipogenesis, together with the actively growing extensions into the cord and the rapid progression, certainly justifies the desig-

35. Henneberg, R.: Ueber Geschwülste der hinteren Schliessungslinie des Rückenmarks, Berl. klin. Wchnschr. 58:1289-1293 (Oct. 31) 1921.

nation of liposarcoma. In a single instance (case 2 of this series) tissue suspected of being myxomatous was present.

Granted that the tumor described by Ritter was malignant, were not some of the other tumors malignant, too? Turner's was the only one so described by the author. It is certain that under the influence of either the lipoma or the factor causing the lipoma the fine strands of pia which normally follow vessels into the cord and the septums which extend into the cord from the pia and the root endoneurium become hyperplastic and increase their cellularity. This invasion of pial connective tissue within the neural tube seems to have some of the essential characteristics of malignancy. The tissue appears to be proliferating, though ever so slowly, and the invasion is so pronounced as to make impossible complete local eradication.

The one question on which, it seems to us, the problem of malignancy turns is whether or not these hyperplastic extensions cause destruction of the tissue of the cord. At first glance it seems as though they did, but it must be remembered that no case is pertinent to this discussion if pressure on the cord by the mass of the tumor went unrelieved before destruction of the cord was already present. In cases in which both the invasion and the pressure operate, it is impossible to say which was the cause of the destruction. If one could answer affirmatively the question whether after the almost complete removal of the lipomatous mass the fibrous extensions into the cord continue to grow and to destroy the cord in the absence of recurrence of a pressure-producing mass the process would have to be considered malignant. There is, however, no case in which such an answer can be given. Indeed, certain cases tend to indicate that destruction of the cord does not proceed after removal of the pressure. In the case of Kernohan, Woltman and Adson relief from pressure on the cord was effected by partial removal of the tumor and wide laminectomy, and the condition, instead of continuing to grow worse, became entirely normal and began to regress only after an interval of nine years, when, presumably, the pressure on the cord again became operative.

The validity of this line of thought is greatly diminished because there is no definite evidence that the cord was invaded in the manner under consideration. The cord in case 2 of this series was definitely invaded, and the patient has shown steady improvement over her postoperative condition during the past eight years. Counteracting this result is that in the case reported by Stookey, who secured improvement over a three year period, when regression began. It cannot be said with assurance that any tumor except Ritter's was malignant, and it is our opinion that this cellularity and invasive aspect of the pial extensions into the cord do not constitute malignancy.

Etiologic Aspects of Intradural Lipoma.—The puzzling question of the origin of lipomas in a location ordinarily considered to be devoid of fat cells has received the attention of a number of recent investigators (Ritter [18]; Henneberg [35]; Stookey [21]; Bielschowsky and Valentin [31]; Verga [36]; Krainer [37]; Scherer [38]; Guillain, Bertrand and Salles [26]; Bucy and Gustafson [20]; Jabotinski [22]). As Verga [36] indicated, in speaking of intraspinal and intracranial lipomas as a group, any hypothesis must account not only for the masses of fat within the dura mater but for the constant intimate relation of the tumors to the pia mater, the connective tissue stroma (sometimes osseous in cases of intracerebral lipoma), the frequent association with anomalies of development and the preponderant location in the midline. To these features should be added the predilection for the cervicothoracic junction of the cord and for the dorsal surface of the cord, the frequent early onset and the notable potentiality for growth within the entering posterior roots. It is our opinion that the iron filing effect cannot be explained satisfactorily by invasion of the root from without. No cells visible in these regions appear capable of such an invasion. The fat must be considered to have arisen within the root at the same time as, and as an inseparable feature of, the rest of the fatty mass.

It was shown long ago that, contrary to appearances, the leptomeninges actually do contain small amounts of fat, and Virchow,[39] in 1863, availed himself of this knowledge to explain intradural lipomas, for it was his expressed view that these growths arose from these self same fat cells. As a larger number of cases accumulated, it became apparent that the great majority of lipomas, especially of the brain, occurred in sagittal locations, whereas if any fat cells in the pia were able to proliferate on occasion this distribution should not obtain. Neither does this hypothesis apply satisfactorily to spinal lipomas, none of which have been reported to occur on the anterior sur-

36. Verga, P., cited by Sperling and Alpers.[1]

37. Krainer, L.: Die Hirn- und Rückenmarkslipome, Virchows Arch. f. path. Anat. **295**:107-142 (July 8) 1935.

38. Scherer, E.: (*a*) Ueber die pialen Lipome des Gehirns: Beitrag eines Falles von ausgedehnter meningealer Lipomatose einen Grosshirnhemisphäre bei Mikrogyrie, Ztschr. f. d. ges Neurol. u. Psychiat. **154**: 45-61, 1935; (*b*) footnote 25.

39. Virchow, R., cited by Sperling and Alpers.[1]

face of the cord. The crucial point against Virchow's hypothesis is that adult fat cells do not reproduce themselves (Wells [40]) and that, whatever adult fat cells come from, it is not other adult fat cells.

A second concept was that of Rindfleisch,[41] who described lipomas originating through deposition of fat in newly formed cell aggregates deriving from the connective tissue. He did not associate formation of fat with primitive cells but, rather stated that it is a property of common connective tissue to proliferate and then to become adipose. Unexplained by this hypothesis is the predilection for sagittal locations in the brain and dorsal locations in the cord. Furthermore, fibroblastic cells are probably differentiated cells incapable of giving rise to other types (Maximow and Bloom [42]). Wilson, Bartle and Dean [43] expressed the opinion, however, that the tumor they had described arose through metaplasia of the adult connective tissue of the pia.

A third possibility, briefly mentioned by Gowers, and then dismissed, placed the origin with fatty substances liberated by the degeneration of neural structures.

A fourth hypothesis (Taubner [44]) placed the parentage with glia cells which proliferate and undergo fatty degeneration. Stookey [21] briefly considered a somewhat similar origin from glia which picks up fat abnormally. Weighty evidence lies against any such origin. The capsule of the lipoma and the septums separating the tumor from the cord have been, without exception, of mesodermal, and not of glial, origin. Glia has never been observed to take up fat in a huge uniglobular manner so as to simulate adipose tissue.

The predilection for sagittal locations has been given such importance by some investigators that they have proposed an origin through inclusion of misplaced elements within the closing lips of the neural groove. Bostroem [45] grouped dermoid, epidermoid and lipoma in the same category as inclusion tumors stemming from embryonic error before the 5 somite stage. Della Rovere [46] expressed the opinion that the inclusions causing lipoma were of mesodermal origin. Ernst [47] stated that some portion of the dermal anlage was sequestered in the closing neural tube. Stookey [21] discussed the pros and cons of this hypothesis in considerable detail, and, though he was not entirely satisfied with it, he accepted it as the best of the explanations available at the time.

The very fact that this hypothesis is formulated particularly to explain the sagitally located tumors proves to be its greatest weakness, for while it well explains the tumors in the midline, it is so inflexible that tumors not in the midline must be accounted for on some other basis. How, for instance, may one explain the bilateral lipoma of the medulla lying in the cerebellopontile angle which was observed by Wolbach and Millet or the 2 tumors of Elsberg,[24] which arose from the portion of the cord anterior to the posterior roots, or the many other laterally, or even ventrally, placed lipomas (Misch [48])?

Furthermore, these lipomas are never surrounded by cord tissue, as one would expect if their anlages had been able to get within the closing neural tube. In a single case (Jabotinski's) a portion of the fat was truly intramedullary. These lipomas, lying in the pia as they do, are of, but not in, the cord. This location seems to speak against their having developed from any germ within the neural tube.

In association with spina bifida fatty masses are seen which may arise by the inclusion of fat precursor tissue within the sclerotomes before the neural arch closes, but the absence of extensive spina bifida in the cases in which there are huge intraspinal lipomas speaks against the hypothesis of inclusion as applying to the latter group. Closure of the neural arch is a sensitive process and is liable to interference by minor disturbances, many not even giving rise to clinically detectable lesions, as in the case of spina bifida occulta. That a mass of tissue could become misplaced between the closing neural arches without causing them to stay open seems unlikely. The absence of dural attachments in almost every case is also against such an origin for these tumors. An argument applicable only against the hypothesis of epiblastic inclusion is the constant absence of any ectodermal tissue in the lipomas, except for the infiltrated cord and the nerve roots. The observation that a variety of

40. Wells, H. G.: Adipose Tissue, a Neglected Subject, J. A. M. A. **114**:2177-2283 (June 1) 1940.

41. Rindfleisch, E.: A Manual of Pathological Histology to Serve as an Introduction to the Study of Morbid Anatomy, translated by E. B. Baxter, London, New Sydenham Society, 1872, vol. 1, p. 168.

42. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

43. Wilson, G.; Bartle, H., Jr., and Dean, J. S.: Intradural Spinal Lipomas, J. Nerv. & Ment. Dis. **91**: 745-753 (June) 1940.

44. Taubner, cited by Sperling and Alpers.[1]

45. Bostroem, E., cited by Sperling and Alpers.[1]

46. della Rovere, D., cited by Ritter [18] and by Stookey.[21]

47. Ernst, P., cited by Sperling and Alpers.[1]

48. Misch, W.: Meningeal Lipomas in the Foramen Magnum, J. Neurol. & Psychopath. **16**:123-129 (Oct.) 1935.

congenital defects are present in cases of intradural lipoma cannot be marshaled as evidence in support of the inclusion hypothesis alone, for it equally supports any hypothesis assuming an origin in defective embryogenesis, whether it is misplacement, abnormal persistence or abnormal differentiation of the anlage.

Another hypothesis of the origin of pial lipomas, advanced by Verga, attributes them to embryonic mesenchyme persisting from the early stages of primitive meningeal formation, which then forms the aberrant lipomatous growths. Krainer reached much the same conclusion, but with embellishments. He concluded that these lipomas were not primarily independent growths; rather, he said that they were malformations of some element in the primitive meninx which, though it differentiated abnormally, continued to behave like the meninx toward vessels and nerves. By this he meant that the fatty masses do not expand and displace nerves and roots, with regard for nothing but their own enlargement. It is as though some part of the primitive meninx, through an unknown defect, oriented its differentiation toward adipose tissue rather than toward fibrous connective tissue. Since the normal pia admits the posterior roots through the pial ring and continues out within the nerve as endoneurium, the adipose pia does likewise. Whatever independent growth the tumor shows is secondary. This hypothesis is attractive, for a number of reasons. It harmonizes with the intrapial location of the tumors and, especially, with the growth within the roots. The shortcomings of the hypothesis are its lack of specificity concerning the exact cells responsible for the formation of the fat, the cause of this formation and its failure to explain the predilection for the cervicothoracic region of the cord.

The possibility of origin in a fat embolus was embodied in a question put to Stookey [21] by Dr. Beverley Tucker during the discussion which followed the presentation of his paper. It has not been considered since.

The most recent proposal is that of Scherer,[38a] who adapted Wassermann's [49] researches on the origin of adipose tissue to pial lipoma. Contrary to the view expressed by Flemming [50] and other investigators that the fat cells are derived from fibroblasts, Wassermann confirmed the hypothesis of Toldt [51] that fat is a specific tissue derived independently of the fibroblasts. In early embryogenesis, when the capillary net is developing in mesenchymal reticulum, the embryonic vessels are surrounded by primitive mesenchymal elements, some of which persist and later give rise to the primitive fat organs which form the nucleus of the fatty lobes and adipose tissue of later life. Adipose tissue is thereby closely related to formation of vessels and is to be considered a part of the reticuloendothelial system. Capillaries are of course everywhere, and the formation of a lipoma becomes easily explicable. This simple hypothesis fails to explain satisfactorily the predilection of lipomas for certain locations, their rarity in a vascular membrane, such as the pia, and the association with other anomalies.

Is it possible to formulate a hypothesis which will explain all the observed facts about these lesions, square with the newer concepts of meningeal origin and fat formation and harmonize, to some extent, the various hypotheses already considered? The following hypothesis seems to do so.

The divergent views of investigators who would derive the meningeal investment entirely from mesoderm (Weed [52]; Flexner [53]) and of others who would assign to the neural crest an important part in the genesis of these structures (Harvey and Burr [54]; Harvey, Burr and Van Campenhout [55]; Raven [56]) seem now to be resolved. The neural tube is early invested by the circumferentially flowing mesenchyme of ectodermal origin—the neural crest. This leptomeningeal anlage is not of single derivation, for mesodermal tissue—endodermal mesenchyme—mingles with it. Before long these two mesenchymes lose their distinguishing characteristics

49. Wassermann, F.: Die Fettorgane des Menschen. Entwicklung, Bau und systematische Stellung des sogenannten Fettgewebes, Ztschr. f. Zellforsch. u. mikr. Anat. **3**:235-328 (Feb.) 1926.

50. Flemming, W., cited by Bell, E. T.: I. On the Occurrence of Fat in the Epithelium, Cartilage and Muscle Fibers of the Ox; II. On the Histogenesis of the Adipose Tissue of the Ox, Am. J. Anat. **9**:401-438, 1909.

51. Toldt, C., cited by Bell, E. T.: I. On the Occurrence of Fat in the Epithelium, Cartilage and Muscle Fibers of the Ox; II. On the Histogenesis of the Adipose Tissue of the Ox, Am. J. Anat. **9**:401-438, 1909.

52. Weed, L. H.: The Development of the Cerebro-Spinal Spaces in Pig and in Man, Washington, D. C., Carnegie Institution of Washington, 1917.

53. Flexner, L. B.: The Development of the Meninges in Amphibia: A Study of Normal and Experimental Animals, Washington, D. C., Carnegie Institution of Washington, 1929.

54. Harvey, S. C., and Burr, H. S.: The Development of the Meninges, Arch. Neurol. & Psychiat. **15**: 545-565 (April) 1926.

55. Harvey, S. C.; Burr, H. S., and Van Campenhout, E.: Development of the Meninges: Further Experiments, Arch. Neurol. & Psychiat. **29**:683-690 (April) 1933.

56. Raven, C. P.: Zur Entwicklung der Ganglienleiste: V. Ueber die Differenzierung des Rumpfganglienleisten-materials, Arch. f. Entwcklngsmechn. d. Organ. **134**:122-146 (March 9) 1936.

and become more differentiated in their progress toward the adult pia-arachnoid. Further differentiation is dependent on the extramedullary passage of ventricular fluid. The surrounding mesoderm forms the dural lamina, but even this is not pure endodermal mesenchyme, for neural crest elements contribute to it.

Whether the vascularization of this compound pial anlage is accompanied by invasion of vessels from without or by formation of capillaries within its substance is of no importance to this discussion. The point is that both the pial anlage and the surrounding mesenchyme are of compound origin and become a more differentiated tissue composed of an apparently single element before vessels appear in the pia. Any fat appearing in the meninges must come from mesenchymal cells persisting around the capillaries. These mesenchymal cells are somehow prevented from forming fat in all but a few cases, and it may be hypothesized that this potentiality is almost completely held in abeyance by some local peculiarity of the tissue resided in. Perhaps the presence of mesenchyme of ectodermal origin exerts this influence. Formation of fat in other organs and locations is held in check for reasons which must be resident in the specific locations. The check on formation of fat fails because of some deficiency of the crest elements in the developing pia in certain locations. That this deficiency is but a part of a more or less generalized defect of ectoderm is suggested by the occurrence of other congenital defects, almost all of which originate in ectodermal faults.

Reasoning from the predominance of subcutaneous lipomas over the upper part of the back, the shoulders and the neck and the location in these segments of the interscapular gland of some animals (Geschickter [17]), one may say that the potentiality for formation of adipose tissue in these segments is greater and the orientation toward formation of fat in the pia of these segments is stronger than in other locations because of its derivation from similar mesenchyme, and consequently it more often overcomes the checking influence. The predominantly dorsal location on the cord and the failure of the fat to encircle the cord completely may be due to the fanning out of the crest elements as they flow around the cord, so that as more anterior positions are reached the deficient region is adequately covered by nondefective crest from adjacent segments. This hypothesis explains the intimate association of fat in roots because the roots penetrate a pia destined to become adipose and the fat actually develops in the pial ring and endoneurium. The hyperplastic nature of the strands invading the cord from the inner surface of the septum separating the cord from the tumor is perhaps to be regarded as a preparation for transformation into adipose tissue. Formation of fat in these strands is an observed fact.

Whether this panniculus adiposus of the pia is to be regarded as a neoplasm or as a malformation, as Krainer would have it, is a difficult question. The tumor described by Braubach did not respect the nerve roots, for it displaced them anteriorly and, though these root fibers were said not to be severely degenerated, the arm served by them was paralytic. Certain tumors (Ritter; Oppenheim and Borchardt; Stookey; Bucy and Gustafson) had free poles, a feature indicating that the fatty mass increased in a longitudinal direction so that it spilled over the ends of the region giving rise to it. This may or may not indicate independent growth. If we may disregard for the moment the question of independent growth, it appears to us that there is no essential difference between the formation of fat in greatly abnormal amounts in the pia and the formation of an abnormal mass of fat in the subcutaneous tissue. Both processes require the proliferation of fat precursor cells and subsequent differentiation into the adult type. Both processes imply a failure of regulatory activity. From a philosophic point of view both masses are to be regarded as neoplasms.

EXTRADURAL LIPOMA

The cases of fatty tumors lying outside the dura are neither so numerous nor so adequately reported as cases of the intradural variety. A large percentage were reported during the previous century, and there has been no increase in the number of cases recorded recently, such as was observed with the tumors inside the dura. This perhaps is to be explained by the fact that there has been a recent renewal of interest in the formation and nature of the leptomeninges and fatty tumors in this location are regarded as of special significance. Extradural lipoma, however, is of a commoner cut, needing no special explanation, exciting less interest and more often going unreported.

Table 2 lists the cases of extradural lipoma in chronologic order. Additional data on 3 cases of extradural lipoma observed at the Mayo Clinic (cases 18, 19 and 20 of table 2) follow.

CASE 5.—A man aged 49, a merchant, registered at the clinic on May 6, 1912, with the complaints of weakness of the legs associated with spasms which doubled up the legs, pain in the back which extended around the body and difficulty in starting the flow of urine.

The family history and the patient's previous medical history were noncontributory. The trouble had begun

TABLE 2.—*Data on Twenty Cases of Extradural Lipomas*

	Year	Author	Sex	Age of Onset, Yr.	Duration	Level	Spinal Puncture	Roentgenographic Changes	Other Disorders	Pathologic Change	Outcome
1	1834	Robarts [57]	F	24	5 yr.	T10 to T12	.....	.....	.....	Fatty tumor	Necropsy
2	1847	Chapelle: Bull. Soc. anat. de Paris **22**: 6-7 (Jan.-Feb.) 1847	F	2½	1½ yr.	Entire spinal cord; greatest at conus	.....	.....	Obesity	Adult fat	Necropsy
3	1847	Albers, J. F. H., cited by Stookey [21].....	..	..	.....	.....	.....	.....	.....	Lipoma	Necropsy
4	1852	Obré: Tr. Path. Soc. London **3**: 248-249 (April 6) 1852	..	1 ?	2 yr.	Upper thoracic; T1 and T2 (?)	.....	.....	.....	Adult fat	Necropsy
5	1857	Virchow, R.: Virchows Arch. f. path. Anat. **11**: 281-288 (March) 1857	M	53	3 mo.	Upper lumbar; L1 and L2 (?)	.....	.....	Multiple similar tumors	Myxomatous lipoma	Necropsy
6	1869	Hoffmann, cited by Stookey [21].....	F	42	9 mo.	Multiple tumors from T7 to sacrum	.....	.....	Other lipomas in dorsal roots; glioma of cord	Adult fat (?)	Necropsy
7	1890	Berenbruch [60]	M	16	2½ mo.	Thoracic (?)	.....	.....	Lipomas of back; angiolipoma of renal capsule; angioma of cord	Angioma with fat cells	Operation; necropsy
8	1895	Starr, M. A.: Am. J. M. Sc. **109**: 613-637 (June) 1895	F	50	4 mo.	T10 and T11; two tumors	.....	.....	.....	Adult fat	Operation; death
9	1897	Strümpell, in discussion on Arch. f. Psychiat. **29**: 1004, 1897	..	..	.....	.....	.....	.....	.....	Adult fat	.....
10	1901	Liebscher, C., cited by Stookey [21].....	F	51	4½ yr.	T7 to T8	.....	.....	.....	Angiolipoma	.....
11	1918	Frazier [10] *	F	55 ?	.....	.....	.....	.....	.....	Angiolipoma	.....
12	1925	Sachs [59] †	M	13	1 yr.	T6 to T7 (?)	.....	.....	Gibbus at level of tumor	Adult fat without capsule	Operation; recovery
13	1925	Pick [58]	F	Young adult	.....	.....	.....	.....	Gibbus at level of tumor	Adult fat (?)	.....
14	1928	Elsberg, C. A.: Surg., Gynec. & Obst. **46**: 1-20 (Jan.) 1928	..	33	3 mo.	T8 to T9 (?)	.....	.....	Multiple lipomas	Embryonic fat	Operation; recovery
15	1929	Kasper and Cowan [61].....	M	6	.....	C2 to T8 and L3 to sacrum; 2 tumors	No block; globulin present	.....	.....	Vascular lipoma	Necropsy; death from lumbar puncture
16	1931	Petit-Dutaillis and Christophe: Rev. neurol. **2**: 821-827 (Dec.) 1931	F	43	1 yr.	T6 to T10	Complete block; 800 mg. of protein per 100 cc.	Bone normal; partial obstruction to iodized poppyseed oil	.....	Angiolipoma	Operation; recovery
17	1939	Ingebrigtsen and Leegaard: Acta chir. Scandinav. **82**: 271-281, 1939	M	22	7 mo.	T7 to T9	.....	.....	.....	Myxolipoma	Operation; recovery
18	1941	Case 5, this series.....	M	48	1 yr.	T9	.....	Spinal column normal	Obesity	Adult fat (?)	Operation; improvement
19	1941	Case 6, this series.....	F	30	3 yr.	T6 to T8	Partial block; 30 mg. of protein per 100 cc.	Spinal column normal	Obesity	Angiolipoma	Operation; recovery
20	1941	Case 7, this series.....	M	67	1 yr.	T8 to T9	Partial block; 75 mg. of protein per 100 cc.	Spinal column normal	.....	Angiolipoma	Operation; recovery

* This report tabulated 2 angiolipomas. One may have been Liebscher's, but the other was not previously reported; we here include it with the information available.
† Sachs did not consider this a lipoma, but it continued to increase in size after it had fulfilled the function ascribed to it. It compressed the cord, and we consider it lipomatous for our purposes.

one year prior to registration in the clinic, when the right leg became weak for three weeks and then returned to normal. Six months before registration the left leg began to weaken and in three months became so weak that the assistance of a cane was required in walking. A month later the right leg again became weak, and the patient was soon unable to stand. Then there developed flexor spasms in the leg and a pain in the back, which extended about the body. No mention was made of exaggeration of this pain at night or on straining. Soon all voluntary motion had departed from the legs. Constipation and the urinary difficulty completed the picture. The weight had dropped from 220 to 165 pounds (100 to 84 Kg.) in an unstated period.

Examination revealed a painful zone over the mid-thoracic spinous processes, a sensory level at the ninth thoracic dermatome below which touch was normal but appreciation of heat and cold was absent, severe spastic paraplegia, increased patellar and achilles reflexes, ankle clonus and a Babinski sign bilaterally. Roentgenograms of the spinal column revealed nothing abnormal.

On May 16, 1912 laminectomy of the fifth to the eighth thoracic vertebrae was performed. Just as the lower part of the incision was being dealt with in a location where the intraspinal contents seemed enlarged, the patient's condition became alarming and the incision was closed. Eight days later additional neural arches, extending from the lower end of the previous incision, were removed, together with an extradural lipoma.

The surgeon was inclined to be hesitant in ascribing the trouble to this fatty mass, but four years later the patient reported that he had had steady improvement and was walking with a cane. Laxatives were required, but he had good vesical and rectal control. Slight numbness was present in the legs. The spasms had disappeared. The eventual outcome is unknown.

The specimen is no longer available, and no description of the tumor was given except that it was called a lipoma.

CASE 6.—A white woman aged 33, a housewife, registered at the clinic on Aug. 2, 1933, with the complaint of weakness of the legs, urinary urgency and numbness extending to the waist.

The family history was of possible significance. Obesity was a trait of the patient's maternal ancestors. One sister was obese, and her mother died of diabetes and paralysis. The patient weighed only 98 pounds (44 Kg.) when she married, but with each of four pregnancies she gained 20 to 30 pounds (9 to 14 Kg.), and at the time of registration she weighed 202 pounds (92 Kg.), although she was short.

The patient's trouble had had its onset on Dec. 28, 1930, at which time she was in the third trimester of pregnancy. While she was attending her mother's funeral her feet became numb. This numbness slowly increased but did not occasion any alarm until Feb. 4, 1931, when, during parturition, she suddenly lost all sensation and motion from the upper part of the abdomen down. A week and a half later there was no improvement, and the patient was told that she could never recover. The next day she could wiggle her toes. By May 1931 her condition had improved to such an extent that her feet merely felt heavy and slightly numb, and she was able to do all her own work. This status obtained until December 1932, when she suddenly became numb to the waist. Increasing paraparesis and urinary urgency began soon afterward.

The results of physical examination were unremarkable except for the obesity and the neurologic signs. There was complete anesthesia from the costal margin down except for an area of seemingly normal sensitivity in the right lower sacral and coccygeal dermatomes and areas of only moderately diminished sensitivity over the lower portion of each calf and the posterolateral aspect of the left hip and thigh. Joint and vibratory sensibilities were absent as high as the iliac spines. Power in the legs was moderately diminished, without any particular muscle groups being selectively affected. The abdominal reflexes were absent. A Babinski sign was obtained bilaterally. The patellar and achilles reflexes were moderately hyperactive but equal on the two sides. There was no clonus. The heel to knee and the Romberg test gave results indicative of disturbance of the proprioceptive sense. The tone of the anal sphincter was normal.

Roentgenograms of the spinal column and thorax revealed nothing abnormal, and results of routine examination of the blood, urinalysis and flocculation tests were normal. Lumbar puncture revealed an initial pressure of 12 cm. of fluid, and the pressure rose to 36 cm. after ten seconds of jugular compression. Ten seconds after release of the compression the pressure was 30 cm.; after an additional ten seconds it was 28 cm., and it then fell to 7 cm. The protein amounted to 30 mg. per hundred cubic centimeters of cerebrospinal fluid.

On Aug. 8, 1933, 4 cc. of iodized poppyseed oil was injected into the lumbar subarachnoid space, and a complete obstruction was demonstrated at the level of the eighth thoracic vertebra. The following day laminectomy of the eighth to the sixth thoracic vertebrae was performed, and a reddish yellow mass, 10 cm. long, 2.5 cm. wide and 1.5 cm. deep, was observed on the posterior surface of the dura. The dura was very thin under the mass, and the cord seemed to be flattened to about two-thirds the normal thickness. The tumor and the surrounding bone were vascular. Total removal of the tumor was effected.

Twenty days after the operation the patient estimated her motor improvement at 25 per cent and her sensory return at 75 per cent. Examination demonstrated that appreciation of light touch had returned to normal in all areas, while pain and temperature sensibilities had improved greatly. Joint sense was normal, but vibratory sense was greatly reduced over the right ankle. The tendon reflexes were the same as before. The abdominal reflexes were barely elicited, and the Babinski sign could no longer be obtained on the right side. Examination a year later revealed that her neurologic condition was normal. A letter from her, dated Sept. 8, 1943, stated that she had been doing all her own work since the operation and that she was free of symptoms except for mild lameness in the back and occasional sick headaches.

The tumor was of soft consistency, and its surface was traversed by delicate fibrous strands. The gross and microscopic features were the same in all parts of the tumor. The sections showed that the tumor was composed of a mixture of fatty and vascular elements (fig. 7*a*). It is estimated that the fatty tissue constituted two thirds and the vascular tissue one third of the tumor. The vessels were mostly the size of small veins, and their walls were invariably thin, being composed of slender collagenous bands, bearing a few fibrocytic cells oriented with the circumference of the vessels. The attenuated walls of the fat cells lying between the vessels made dichotomous junctions with the walls of the vessels. In a number of locations, especially where the vessels lay close to one another

and were not separated by fat, the vessels were observed to be connected by light collagenous tissue bearing cells with lightly stained cytoplasm and oval to elongate vesicular nuclei. A few small arteries and arterioles were evident in the tumor, and a few fibrous septums partitioned the tumor in an incomplete fashion. These septums were unremarkable histologically and were unobtrusive. The fat cells which filled the spaces between the vessels were all of adult adipose tissue type and no embryonic, xanthomatous or myxomatous regions or cells were present.

CASE 7.—A man aged 68, a railway coach carpenter, registered at the clinic on Oct. 5, 1942, complaining of burning sensations and progressive weakness and incoordination of the legs and swelling of the feet toward the end of the day.

The family history and the patient's previous medical history were unimportant. The swelling of the feet had begun in September 1941; it had not been bothersome, had affected the right foot more than the left and had not been associated with other symptoms until April 1942, when the burning sensation appeared in the right foot. In a few weeks the left foot began to burn similarly, and in a few more weeks the burning ascended both legs to the groins. This sensation was more severe on the anterior than on the posterior aspects of the legs. The soles of the feet felt as though he were walking barefooted on cinders. In June 1942 weakness and lack of coordination of the legs made their appearance and steadily increased in severity. The right leg had given more trouble than the left. Examination did not reveal signs of significance except in the nervous system. Cutaneous sensibilities were moderately diminished over both legs. Vibratory anesthesia was complete to the iliac crests, while joint sense was greatly diminished in the toes of the right foot and less so in the toes of the left foot. The gait was of spastic type, and ataxia was prominent. The right leg was demonstrably weakened and spastic, but not so the left leg. The patellar reflexes were increased but equal on the two sides. The achilles reflexes were unequal on the two sides, the response on the right side being the stronger. The Babinski sign was present bilaterally, being stronger on the right side than on the left.

Roentgenograms of the spinal column revealed nothing significant. On lumbar puncture the rapid rise but slow fall of the fluid suggested a partial block. The spinal fluid was colorless; the serologic reactions were negative, and the total protein amounted to 75 mg. per hundred cubic centimeters of fluid. After the lumbar puncture vague impairment of sensation appeared below the twelfth thoracic dermatome. Iodized poppyseed oil injected into the caudal subarachnoid space demonstrated a protruded disk at the first lumbar interspace on the left side and complete obstruction to the upward passage of the oil at the level of the eighth thoracic vertebra, apparently due to a mass lying dorsal to the cord.

On October 16 laminectomy of the eighth and ninth thoracic vertebrae was performed with local infiltration anesthesia, and a soft, reddish yellow, extradural tumor, measuring 2 by 3 cm., was exposed. This was easily separated from the dura, and the incision was closed after immediate examination of frozen tissue had revealed a vascular lipoma.

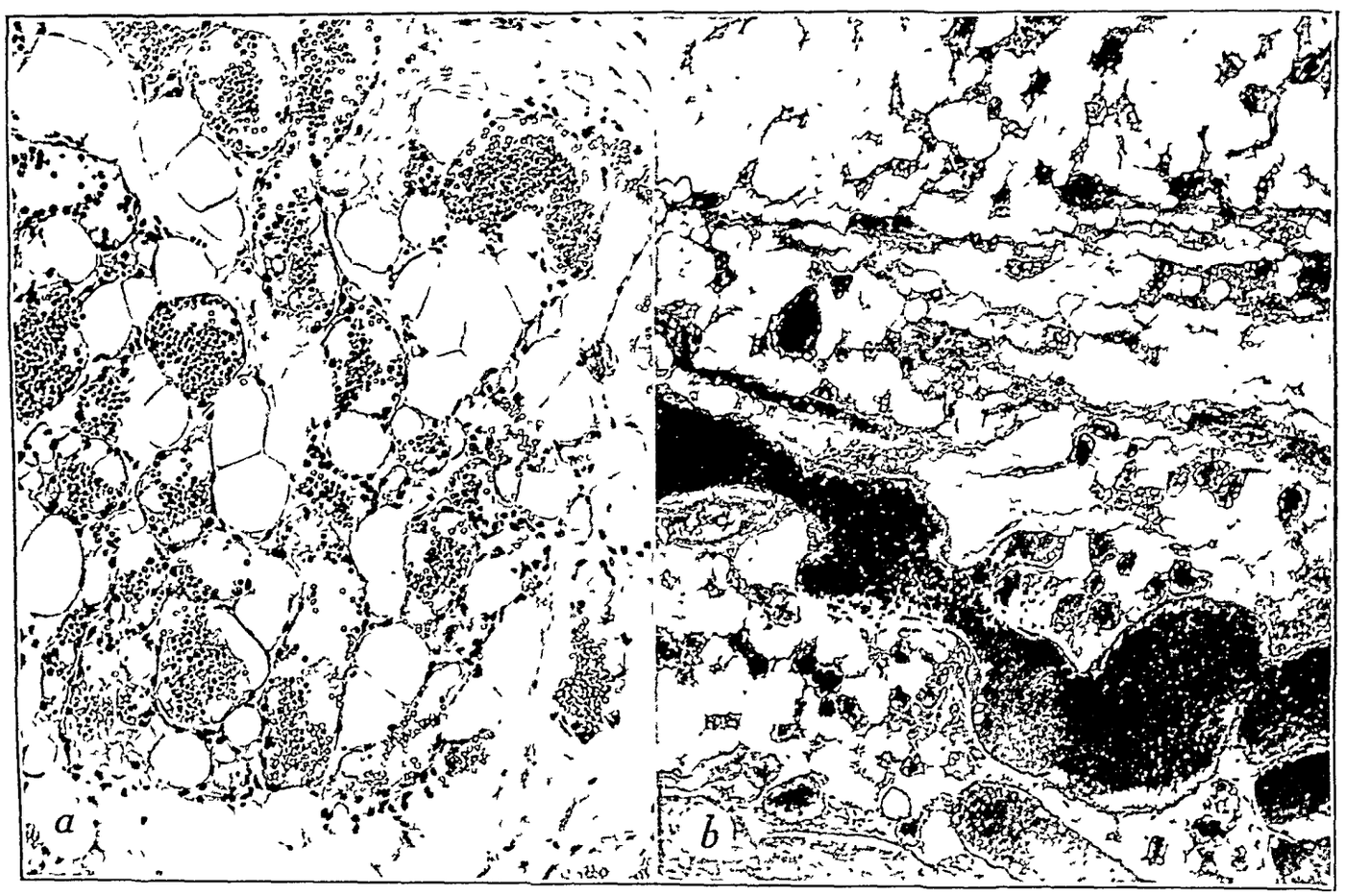

Fig. 7.—(*a*) Extradural lipoma (case 6), showing small, thin-walled cavernous blood spaces interspersed with adipose tissue of adult type (hematoxylin and eosin stain; × 150). (*b*) Extradural lipoma (case 7), showing its angiomatous and lipomatous nature. The vessel walls are slightly thicker; the variation in the size of the vessels is greater, and there is more connective tissue present than with the tumor shown in *a* (hematoxylin and eosin; × 45).

Neurologic examination on October 29 showed only diminution of appreciation of touch, pain and temperature on the lateral aspects of both thighs, moderate diminution of vibratory and joint senses in the legs and a weak Babinski sign bilaterally. Strength in both legs was normal; the tendon reflexes were equal on the two sides, but the patellar reflexes seemed somewhat hyperactive. A recent letter indicated that recovery has been complete.

The surgical specimen was without external markings of note. The histologic appearance of this tumor closely approximated that of the tumor in case 6 except that the vessels displayed more variation of size and the tumor was distinctly more cellular in places. There were areas where the mixture of fat and vessels corresponded to the appearance of the tumor in case 6. In other regions the character of the tumor approximated that of a cavernous hemangioma, with large dilated, tortuous blood spaces separated by but little fat (fig. 7*b*). In other locations the tumor was more cellular, and small vessels or blood spaces gave it a distinctly hemangioendotheliomatous aspect. Some of these small blood spaces accommodated but one or a few erythrocytes. No xanthomatous or embryonic fat cells were present. In numerous locations scattered throughout the tumor the adipose stroma widened to become a patch of cellular tissue, seeming capable of activity. The ground material in these regions consisted of a loose arrangement of fibrous strands and reticulin, in which there appeared a few lacunas containing erythrocytes. The cells of this tissue were fusiform and contained oval, elongated or crescentic nuclei, which stained more lightly than the fibrocytic nuclei. There were no mitoses, and one searched in vain for new formation of fat. All the fat-containing cells were typical adult cells filled with a single large globule of fat.

Clinical Features of Extradural Lipoma.—The 17 cases of extradural tumor found in the literature and the 3 cases reported in the present series make a total of 20 cases available for collation. On the basis of reported cases, therefore, extradural lipoma appears to be even rarer than intradural lipoma.

The sex of 4 patients was not stated. Of the remaining 16 patients, 7 were males and 9 females. Extradural lipoma seems not to favor any age, for it occurs with about equal incidence throughout the life span. The youngest patient was 1 year old and the oldest almost 70 (fig. 3). The duration of symptoms was rather short (fig. 4). Robarts'[57] patient had had symptoms for five years, and this was the longest duration in the entire series. Many of the patients had had trouble for but a few months. Only 4 had a history extending back two years or more. The median duration was about one year.

The outstanding complaint was one of weakness of the legs. Girdle pains were prominent in the recital of symptoms in 3 cases. The results of physical examination were unremarkable on the whole. In 1 case (case 5 of the present series) a peculiar dissociation of sensation was exhibited; the temperature sense was absent below the ninth thoracic dermatome, but the sense of touch was everywhere normal. Spinal puncture was performed in 4 cases. In 3 of these cases examination revealed a manometric block. In the 1 instance in which the manometric reading was normal the fluid contained globulin. In 2 of the 3 cases in which fluid was obtained in the presence of obstruction the protein content was increased; in the other case the protein was normal.

In few of the cases of extradural lipoma were there congenital defects. In 2 cases (Pick[58]; Sachs[59]) severe kyphosis developed after birth, and in each instance the angle of the gibbus was over the level of the tumor. It is not certain, however, that these 2 cases do not represent some other condition. In Berenbruch's[60] case the patient was born with one lipoma and one vascular lipoma, both in superficial locations. In 3 cases the patient was obese, and in 1 of these cases there was a history of obese maternal forebears. We have no assurance that obesity was not present in some of the other cases. In 3 cases disturbances of formation of adipose tissue or of fat metabolism were evidenced by "generalized lipomatosis" (multiple lipomatosis[?]), by multiple myxomatous lipomas and by lipomas of the dorsal roots.

The method used in assessing the segmental distribution of the intradural lipomas was resorted to with the extradural variety. The conclusions to be drawn from figure 8 are evident. In only 2 cases did the tumor not lie, at least in part, in the thoracic portion of the spinal canal. The 3 larger tumors extended above and below the thoracic portion, but their greatest extent was within this portion of the canal. The sixth to the ninth thoracic segments were the areas most often affected. Nearly all the extradural lipomas developed on the dorsal aspect of the dura.

In gross and histologic features extradural lipoma is unlike intradural lipoma. Half of the 20 tumors were definitely or presumably of ordinary adipose tissue. Many of these tumors were described long ago, without histologic study. The remaining 10 tumors were of three types: Seven were mixtures of adult fat and vessels of various sizes and quantities. One of these (Beren-

57. Robarts, H. P.: Case of Disease of the Spinal Cord with Observations, London M. Gaz. **13**:946-950 (March 22) 1834.

58. Pick, L., cited by Sachs.[59]

59. Sachs, E.: An Unusual Case of Paraplegia Associated with Marked Gibbus and a Localized Collection of Fat at the Site of the Gibbus, J. Bone & Joint Surg. **7**:709-719 (July) 1925.

60. Berenbruch, K., cited by Stookey.[21]

bruch [60]) was an angioma with fat dispersed through it. Another (Kasper and Cowan [61]) was described as a lipoma with moderately large, blood-filled vessels. Five tumors were mixtures of angioma and lipoma in such proportions as to be best characterized as angiolipomas. Figure 7 shows the justice of this designation. Two tumors were mixtures of adipose tissue and myxomatous material. One tumor was said to be of embryonic fat, but no further description was given. As mentioned before, the photomicrograph presented with this case suggests that myxomatous material was also present.

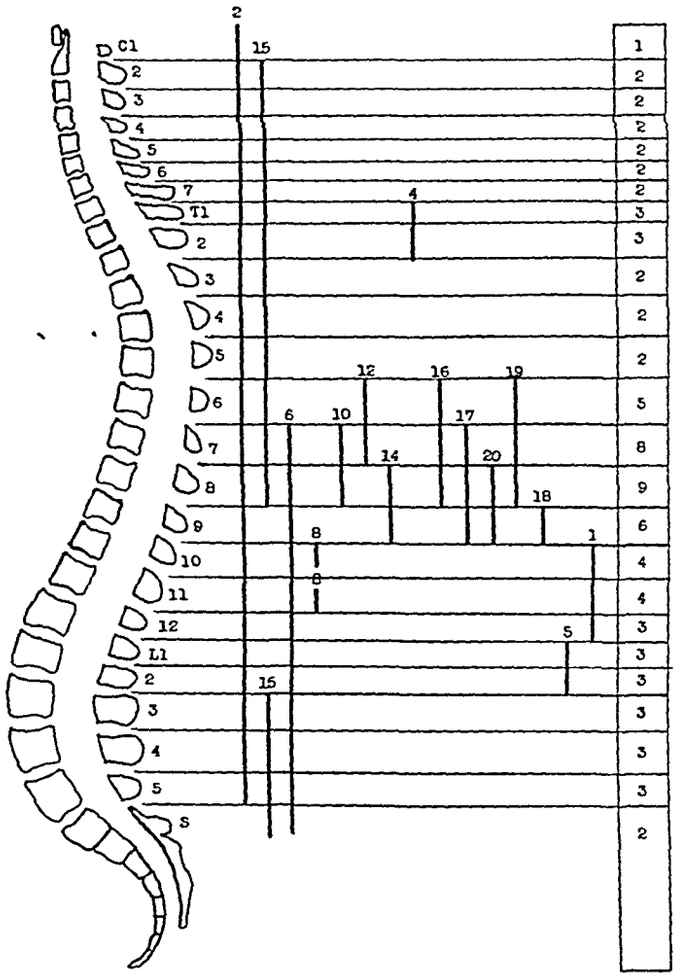

Fig. 8.—Longitudinal distribution of the extradural lipomas with reference to the spinal column. The numbers at the top of the tumors refer to the cases as enumerated in table 2. The column at the right indicates the total number of times each segment is involved by tumor. The tumor numbered 16 extended two segments farther down than is indicated.

Etiologic Factors of Extradural Lipoma.—Little is to be found in the literature concerning the genesis of lipoma from the extradural fat. Robarts speculated that the tumor reported by him arose in the blood clot supposed to have been produced by the blow to the back sustained two years prior to the onset of symptoms. The remarkable feature of the extradural lipoma is not that it occurs but that it does not occur more often. Though the extradural fat is considered to be less fibrous and more buttery than the subcutaneous fat, there is nothing essentially different about it which would explain the paucity of lipomas originating from it.

The extradural fat is more vascular than the subcutaneous fat, owing to the presence of the meningorachidian veins lying in association with it. The persistence of these vessels into adult life suggests that this tissue was much more vascular in embryonic life before the differentiation of the vascular plexus into the adult form. The researches of Wassermann and others indicating the common origin of the endothelium and the fat organ and the potentiality of the mesenchymal cells about the capillaries of adult life for the development of either vessels or fat have been mentioned. That 7 of 20 extradural lipomas were angiomatous cannot but have significance. It is probable that the lipoma of which we speak originates from certain of these bipotential cells. The disposition of these cells to form vessels is well demonstrated by the angiomatous character of the lipoma, and this angiolipoma points to the common parentage of the pure lipoma and the pure angioma—tumors so different in appearance, yet pathologic brothers.

Three facts must be taken into consideration in any speculations on the etiologic factors concerned with extradural lipoma. First, the tumor does not seem to be of congenital origin because it occurs at all ages and the duration of symptoms is short; it is unlikely therefore that the tumor is present for a long time before giving evidence. Second, the segmental distribution is not that of the intradural lipoma or of subcutaneous lipoma; rather, it is that of the meningioma. Third, in an inordinate number of cases this tumor is associated with obesity and multiple lipoma.

Is this tumor actually a meningioma? A tumor which is a meningioma beyond dispute because of the presence in it of masses of cells of the arachnoid cap type as the principal component may, of course, contain fat. The fat may occur scattered about the tumor and in some regions may be rather heavily deposited, but there is no difficulty in finding other regions in which sheets of plump cells, whorls or psammoma bodies are displayed. Photomicrographs of small regions of lipoblastic meningiomas presented with descriptions of these tumors are likely to be misleading because of the pardonable zeal of the authors to show the fatty parts more effectively.

In no case of the extradural lipoma, on the other hand, did the tumor contain regions of cells

61. Kasper, J. A., and Cowan, A.: Extradural Lioma of the Spinal Canal, Arch. Path. **8**:800-802 Nov.) 1929.

anything like arachnoid cap cells. In case 7 of this series the tumor contained small islands of scattered cells, but they did not appear to warrant one's calling the tumor meningiomatous. The preponderance of the growths in the thoracic region of the spinal column suggests the possibility that the tumor is a meningioma. This is countered by the fact that all the tumors lay on the external surface of the dura, without any penetration of this membrane. No lipomatous tumor has been observed attached to the inner surface of the dura except the 2 pial lipomas, which had secondary attachments and tumors of the type which is indubitably meningioma (Brown [62]), as mentioned previously. A further argument against this lipoma's being a meningioma lies in the absence of recurrence after simple cleavage from the dura without removal of the attachment. The subject of case 6 of this series was well more than ten years after such a removal. Whatever may be the cause of the lipomatous and angiomatous development from the fat, it is probably not any influence of the arachnoid or its derivatives. The occurrence of obesity and multiple lipoma indicates that the cause is to be sought in some abnormality of the fat organ.

CLASSIFICATION

Cornil and Mosinger [63] proposed a classification of six types of intraspinal lipomas based on the relation of the tumors to the intraspinal content: (1) intramedullary lipoma, (2) intradural extramedullary lipoma, (3) extradural lipoma, (4) radicular lipoma, (5) lipoma of the filum terminale and cauda equina and (6) multiple lipoma. At the time of the report by these authors no instance of lipoma of the roots, other than of the cauda equina, was known, and their fourth group was therefore theoretic. Case 3 of this series is an instance of a lipoma of a root in the thoracic region and so brings the fourth group of Cornil and Mosinger into the realm of the actual. Except for clinical purposes, there seems to be no reason for separation of lipomas of the cauda from lipomas of other roots. The tumors are so rare that even on this basis the separation appears undesirable. The intramedullary group become theoretic if the tumor reported by Schmieden and Peiper [11] is considered other than a lipoma, as has been suggested.

62. Brown, M. H.: Intraspinal Meningiomas: A Clinical and Pathologic Study, Arch. Neurol. & Psychiat. **47**:271-292 (Feb.) 1942.

63. Cornil, L., and Mosinger, M.: Des lipomes intrarachidiens, Arch. de med. gén. et colon., 1933, p. 220; book review, Rev. neurol. **1**:634 (April) 1934.

The 49 cases of intraspinal lipoma considered in this paper are capable of rational classification on a combined anatomic and pathologic basis. In this proposed classification each type is more homogeneous than those of Cornil and Mosinger, and certain groups carry implications of clinical and surgical importance. The numbers in parenthesis following the individual types refer to the cases as numbered in tables 1 and 2.

Extradural lipoma
- Tumor of adult adipose tissue (cases 1, 2, 3, 4, 6, 8, 9, 12, 13 and 18)
- Tumor of adult adipose tissue and blood vessels (angiolipoma) (cases 7, 10, 11, 15, 16, 19 and 20)
- Tumor of adipose tissue and myxomatous tissue (myxolipoma) (cases 5 and 17)
- Embryonic lipoma (case 14)

Intradural lipoma
- Massive tumor associated with severe congenital defects (cases 7, 14 and 25)
- Circumscribed pial tumor (cases 2, 3, 5, 6, 8, 10, 11, 12, 13, 16, 18, 19, 20, 21, 22, 23, 24, 26, 27 and 29)
- Tumor of the intradural roots or the filum terminale (cases 4, 17 and 28)
- Liposarcoma (case 9)
- Myolipoma (case 1)

RELATION TO OTHER DISEASES

The relation that the intraspinal lipoma bears to certain other diseases is of interest, and perhaps of some importance with regard to the causation of the related tumor. The probable absence of any relation between the extradural lipoma and the meningioma has already been indicated. Similar conclusions may be drawn concerning the pial lipoma.

The probability that lipoma and angioma are related neoplasms has been mentioned in connection with the causal factors in extradural lipoma. It is strange that the pial lipoma is not sometimes angiomatous, since it arises in a vascular membrane which sometimes gives rise to angiomatous masses. This brings to mind the case reported by Cobb,[64] in which a hemangioma of the medullary pial sheath was accompanied by vascular nevuses of the skin in the dermatome served by the affected segment of the cord. There arises the question of the relation between this occurrence and the instances of pial lipoma accompanied by lipoma overlying the lesion of the cord. These cases seem to indicate the participation of common mesenchyme with an abnormal potentiality for formation of tumor in the genesis of the pia.

64. Cobb, S.: Hemangioma of the Spinal Cord Associated with Skin Naevi of the Same Metamere, Ann. Surg. **62**:641-649 (Dec.) 1915.

Adair, Pack and Farrior[65] drew certain parallels between multiple lipomatosis and the multiple neurofibromatosis of Recklinghausen. They pointed out that the tumors in certain cases of multiple tumors of nerves are not all of one type, some being neurofibromas and some lipomas. On the basis of these cases of mixed tumors and the many similarities between neurofibromatosis and multiple lipomatosis brought out in the present study, it appears that intraspinal lipoma is in this category. Intradural (pial) lipoma originates in part from the endoneurium of nerve roots, which is of the same material as the pia. In rare cases an intradural lipoma arises solely from roots. Extradural lipoma may be accompanied by multiple lipoma. The question is certainly not simplified by the fact that the lipoma actually noted to involve roots by reason of its origin from the endoneurium (pial lipoma) is not accompanied by multiple lipoma in the sense of Adair, Pack and Farrior while the tumor not springing from roots (extradural lipoma) may be so accompanied.

Whatever the relation between lipoma and neurofibroma may be, it is obscure. Neurofibromatosis has been related to tuberous sclerosis, Lindau's disease and Sturge-Weber disease, and the group of diseases has been termed congenital ectodermoses (Yakovlev and Guthrie[66]) and phacomatoses (Brouwer, van der Hoeve and Mahoney[67]). There appear to be reasons for including multiple lipomatosis in the group as a fifth type. The intraspinal lipoma may, therefore, bear some relation to the aforementioned diseases, but that is a subject for future consideration.

SUMMARY AND CONCLUSIONS

Nearly 1 per cent of intraspinal tumors are lipomas. Three fifths of the lipomas are intradural, and two fifths are extradural.

The distribution between the sexes is about equal for the two varieties of intraspinal lipoma.

The onset of symptoms of intradural lipoma, with few exceptions, is before the age of 2 or 3 years, at the beginning of the third decade or at the beginning of the fifth decade. Symptoms of extradural lipoma appear at any age.

The duration of symptoms of intradural lipoma (before death or surgical removal) ranges from a few months to more than fifteen years. The median duration is about four years. The duration of symptoms of extradural lipoma is usually short, the median being about one year.

The clinical expression of intradural lipoma is distinctive for five reasons: (*a*) Definite root pains are uncommon despite the frequent involvement of roots by the tumor; (*b*) ataxia of the extremities due to deficit of position sense is occasionally one of the first manifestations of the lipoma; (*c*) unilateral flaccid paralysis of an arm associated with spastic paralysis of the legs is sometimes observed; (*d*) complete subarachnoid block is unusual despite the large size to which the tumor grows; (*e*) discoverable changes in the spinal roentgenogram may be absent, but, on the other hand, the spinal canal may be widened for a considerable distance.

Intradural lipoma occurs most commonly in the cervicothoracic region of the spinal cord. Extradural lipoma is most common in the lower part of the thoracic region. Both types of lipoma are far more common on the dorsal surface of the structure giving rise to them than on other surfaces.

All but 1 of the intradural lipomas were composed of adult adipose tissue or of adult adipose tissue with excessive fibrous stroma. Only half of the extradural lipomas were of adult adipose tissue; most of the remainder were angiomatous; a few were myxomatous; 1 was of embryonic fat.

Roots traversed the intradural lipoma in most cases, and it was common to see the fat lying in such intimate relation to the finer structures of the root as to lead to the supposition that the fat developed within the root and did not secondarily infiltrate it.

Intradural lipoma is invariably observed to be separated from the neural tissue by a layer of fibrous tissue of pial derivation. A pial sheath covers the free surfaces of the tumor. Therefore the intradural lipoma is of pial origin.

The connective tissues associated with pial lipoma show certain changes of a proliferative nature: (*a*) The endoneurium of traversing roots proliferates to form prominent fibrocellular masses within the lipoma; (*b*) the pial septum between the tumor and the cord thickens and sends heavy extensions into the cord; (*c*) the pial capsule over the surface of the tumor thickens and may become adherent to the arachnoid and dura.

The apparent invasiveness of the connective tissue with regard to the cord is probably not an expression of malignancy.

65. Adair, F. E.; Pack, G. T., and Farrior, J. H.: Lipomas, Am. J. Cancer **16**:1104-1120 (Sept.) 1932.

66. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145-1194 (Dec.) 1931.

67. Brouwer, B.; van der Hoeve, J., and Mahoney, W.: A Fourth Type of Phakomatosis: Sturge-Weber Syndrome, Amsterdam, Uitgevers-Maatschappij, 1937.

Pial lipoma probably arises because of local failure of normal control over formation of fat from the normally present pericapillary mesenchymal cells. In these cells, which have fat-forming potentialities, a panniculus adiposus of the pia proceeds to develop. Whether this is neoplastic or is a "malformation," or whether there is any difference between the two, is an open question.

Extradural lipoma seems to be related to a vague defect of the primitive fat-forming tissue itself.

Neither form of lipoma is related to meningioma.

There is a close relation between lipoma and angioma. Intraspinal lipoma appears to be related to neurofibromatosis and the other "phacomatoses."

Congenital defects are rather often associated with intradural lipoma. Obesity and multiple lipoma occasionally accompany the extradural lipoma.

NOTE.—Since the preparation of this paper, an additional case of intraspinal lipoma has been reported from the Mayo Clinic.[68]

68. Ehni, G. T., and Pugh, D. G.: Intraspinal Lipoma, Proc. Staff Meet., Mayo Clin. **19**:513-515 (Oct. 18) 1944.

The Mayo Clinic.

PHENOMENON OF VISUAL EXTINCTION IN HOMONYMOUS FIELDS AND PSYCHOLOGIC PRINCIPLES INVOLVED

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During World War I a variety of syndromes due to cerebral injuries were described. Among the numerous interesting signs noted was one of "visual inattention in homonymous fields," or "hemianopsic weakness of attention." Poppelreuter [1] observed 7 cases in which the patient was able to perceive only one of two figures or points simultaneously exposed on the sides of a central point of fixation. However, if only one figure was exposed in the "affected field," the image was seen. Head [2] noted this phenomenon in a case of a gunshot wound of the left occipitoparietal cortex, with residual aphasia and a right homonymous field defect, but his description lacks details. Riddoch [3] reported 2 cases of defective attention in the right homonymous fields, and in both instances there was a neoplasm in the angular and supramarginal gyri on the left side. Akelaitis [4] described 2 cases of left and 1 case of right homonymous hemiamblyopia due to head trauma in which attentiveness, as tested by Oppenheim's method, was impaired. Oppenheim [5] suggested that the patient's "attentiveness" be tested by simultaneous exposures to objects at identical points in each homonymous field because some patients fail to appreciate the image on one side, although they could see it if it were exposed alone in the same position.

All these authors assumed that this visual symptom was due to lack of attention on the affected side. Their descriptions are relatively meager, and, as Head stated,[2] "these changes have not been completely investigated." Kluver,[6] in an extensive review of this and allied visual disturbances, made the same intimation. Recently we have studied a case of this type over a long period, and, after careful and detailed observation, we have found that the failure to appreciate an image on one side, as tested by Oppenheim's method, is not due to inattention but is the result of underlying normal psychologic mechanisms. This case and the psychologic principles involved are now reported.

REPORT OF A CASE

A Marine aged 29 was wounded in the right side of the head but was not incapacitated until a missile struck him in the left occipitoparietal region, when he fell unconscious. When he regained consciousness, he found himself in a dugout, unable to speak or move the right side of the body. He was evacuated to a hospital. On examination global aphasia, right hemiplegia and apparent hemianopsia were noted. One week later the hemiplegia had disappeared. A craniotomy was then performed, and fragments of bone were removed from the left side of the head. The underlying occipitoparietal cortex was contused. The patient continued to improve. Within a month the hemianopsia began to recede, and he became more communicative. However, the following significant symptoms lingered during the next two months: (*a*) severe acalculia, (*b*) spelling defect, (*c*) dysgraphia and (*d*) inability to perceive an object on the right when a concomitant stimulus was present in the left field of vision. Spontaneous speech returned. He showed little agrammatism and no anomia. There was no finger agnosia or disorientation for right and left. His greatest defect was in calculation. He had always considered himself good in arithmetic, but twelve weeks after the injury he still was unable to recite the multiplication tables of 2's and 3's accurately. He made errors in simple tests, such as 8 plus 3 and other sums which equated to less than 20. The calculation defect was most marked for subtraction. Often he was unable to recognize the correct solution to the problem even when it was given to him, and he was seldom certain of the answer.

Visual Disturbances.—Ever since the hemianopsia had begun to recede, the patient complained, "If I stare long enough, my vision starts to blur on the right side.

From the United States Naval Hospital, San Diego, Calif.

Presented at the Seventieth Annual Meeting of the American Neurological Association, New York, May 20, 1944.

1. Poppelreuter, W.: Die psychischen Schadigungen durch Kopfschuss im Kriege 1914-1916: Die Störungen der niederen und hoheren Schleistungen durch Verletzungen des Okzipitalhirns, Leipzig, Leopold Voss, 1917, vol. 1.

2. Head, H.: Aphasia and Kindred Disorders of Speech, London, Cambridge University Press, 1926, vol. 1, p. 439; vol. 2, p. 108.

3. Riddoch, G.: Visual Disorientation in Homonymous Half-Fields, Brain **58**:376-382, 1935.

4. Akelaitis, A. J.: Studies on the Corpus Callosum: V. Homonymous Hemiamblyopia Before and After Section of the Corpus Callosum, Arch. Neurol. & Psychiat. **48**:108-118 (July) 1942.

5. Oppenheim, H.: Diseases of the Nervous System, translated by E. E. Mayer, Philadelphia, J. B. Lippincott & Co., 1900, p. 59; Lehrbuch der Nervenkrankheit, ed. 7, Berlin, S. Karger, 1923, p. 1113.

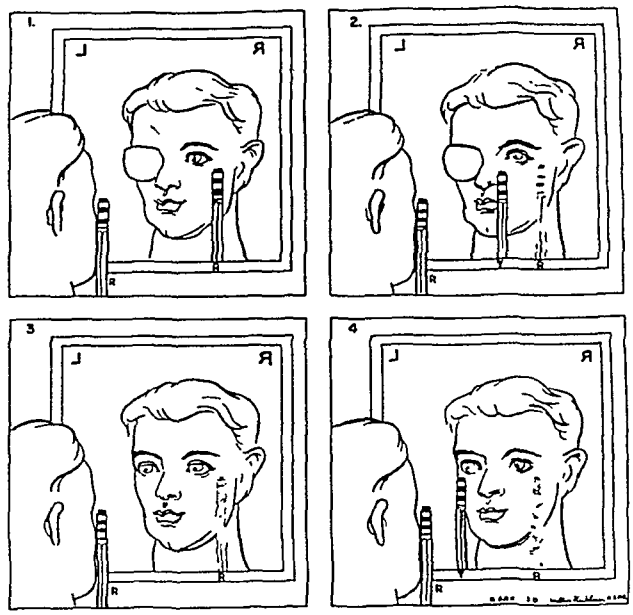
6. Kluver, H.: Visual Disturbances After Cerebral Lesions, Psychol. Bull. **24**:316-358, 1927.

I can't go to the picture show for the same reason. When I first start to read, everything is clear, but then I must stop because the right side blurs. After a rest I can see again. Also, if I look at one object long enough and look away, I still can see it." The last phenomenon was present for one month. Examination revealed that the patient was unable to see in his right homonymous field when an object was exposed simultaneously in the left field of vision. This was true with both uniocular and binocular testing. When the perimetric fields became normal (the last defect noted was for color in the right inferior quadrant) this phenomenon became most apparent. While he was fixating on a central point, the patient clearly perceived the form and color of an object placed in his right field of vision. However, when another object was brought into view on his left side, the image on the right became extinct. This extinction phenomenon was noted on repeated examinations in the right homonymous fields of vision. During the extinction of the image the patient made a strong effort to "see" the object by squinting his eyes and concentrating, but was unsuccessful. However, as soon as the stimulus in the left field was removed, he perceived the exposed object on the right. When tested for separately, the object on the right appeared clear, but sometimes blurred and dull. The object seemed to fluctuate in distinctness.

In time the remaining aphasic symptoms decreased further, although the acalculia was still striking. The visual phenomenon began to change. Fourteen weeks after the injury it was noted that the image in the right field did not always vanish when the left field was stimulated. Instead, it became dull, lost its form and color and appeared shadowy. There was no micropsia or teleopsia. Again, when the stimulus in the left field of vision was removed, the object on the right became more luminous and regained its color and meaning. This was noted irrespective of the degree of likeness or unlikeness in luminosity of the objects exposed in the opposite fields of vision. There was no apparent loss of attention. What there seemed to be was a relative reduction of visual acuity or an obscuration of the visual image (obscuration phenomenon). These phenomena were less apparent the nearer the object in the right field was exposed to the point of fixation.

Sixteen weeks after the injury the following observations were noted: (*a*) On separate tests of all four quadrants, the patient claimed that the image in the right superior homonymous field of vision was clearer than that in the right inferior homonymous field. (*b*) The obscuration phenomenon was much more apparent in the inferior than in the superior quadrant on the right side. Thus, when a pencil was placed in the patient's right inferior field he recognized it, but when another pencil was placed in his left niferior field the one on the right became blurred, dull and shadowy. The same was true when the corresponding superior quadrants were tested, but the difference here was much less apparent than in the comparable lower quadrants. When a long pencil was held vertically in the right field of vision, the patient stated he perceived that part of the pencil in the upper quadrant more clearly than the portion in the lower quadrant. The simultaneous exposure of an object in the same position on the left side produced a further decrease of perception on the right side, particularly in the lower quadrant.

Five months after the injury[7] the patient complained that "on looking in a mirror the right side of my face is sort of blurred. My right eyeball is not clear; but when I cover my left eye, I can see the right eye clearly in the mirror. I can also see the right side of my forehead better than the right side of my jaw." These visual disturbances were well demonstrated by requiring the patient to fixate with one or both eyes in a mirror 30 inches (76 cm.) away under daylight illumination. The test object used in the right lower field of vision was a red pencil placed vertically on the cheek below the outer canthus of the right eye (figure). The detailed observations made under these conditions are listed in table 1. In summary, it appeared that the greater the stimulation in the left fields of vision, the less the patient saw on the right. There was obscuration of form; with sufficient stimulation in the left field even motion could not be perceived on the right.



What the patient sees in the mirror (responses under conditions 1 to 4 in table 1). The red pencil is designated by R, and the yellow pencil, by Y. The patient fixates on one or both eyes and is asked to describe the perceived reflected image of pencils held on one or on both sides of the fixation point. Mirror images of R and L represent the right and left sides of the patient's body. Note that the more stimulation there is in his left field of vision, the more blurred does the image (pencil R) in the right field of vision appear to him.

An interesting observation was the variability of the image perceived in the right field of vision. This fluctuation at times was so pronounced that the results obtained during special visual tests were confusing. However, when these variations in perception were timed, a definite periodicity in fluctuation was noted, as shown in table 2.

7. At this time, when the patient returned from a forty day furlough, he complained that he did not know "what the right hand was doing." Detailed examination of the cutaneous sensory status revealed the following disturbances in his right upper extremity: (1) unawareness of the extremity; (2) fluctuating sensory defects; (3) decrease of cutaneous sensory perception on the right side when the left hand was stimulated simultaneously (cutaneous sensory extinction phenomenon); (4) reduction of sensory adaptation time over the entire right side of the body, and (5) absence of after-sensation on the same side.

TABLE 1.—*Data on Visual Fixation Tests*

Condition	Response
1. Right eye fixated in mirror; left eye closed; red pencil placed on right cheek	Red pencil appeared clear, but image fluctuated in distinctness (table 2)
2. Right eye fixated in mirror; left eye closed; red pencil on right cheek and yellow pencil placed on the nose	Red pencil appeared blurred, but details were still discernible; image of red pencil fluctuated in distinctness and color
3. Binocular fixation in mirror; red pencil on right cheek	Red pencil appeared blurred; details were imperceptible; distinctness of image waxed and waned periodically
4. Binocular fixation in mirror; red pencil on right cheek; yellow pencil on left cheek	Red pencil appeared very blurred, becoming brown and and gray; no details; fluctuation phenomenon apparent, image often disappearing completely
5. Binocular fixation in mirror; red pencil on right cheek; three yellow pencils on left cheek	Form of red pencil was barely recognized; color was imperceptible; notable fluctuation in acuity; at times image and appreciation of movement disappeared; images of pencils on left side clear and nonfluctuant

each eye saw an after-image. However, simultaneous or rapidly successive light stimulation of both eyes (an illuminated vertical line thrown in one eye and a round light in the other) produced a persistent after-image, usually in the left eye. Rarely were there after-images in both eyes at the same time or only in the right eye.

Tachistoscopic Examination: This test, performed seven months after the injury, showed reduction of perception in the right side of the field when the image was exposed for less than one second.

Color Tests: The patient could recognize colors in each of the field quadrants. However, the simultaneous exposure of objects in the two half-fields of vision caused disappearance of the color on the right side (figure). The degree of change depended on the intensity of visual stimulus thrown in the normal field. The more visual stimulus there was on the left side, the less color the patient perceived on the right side. In all instances color ultimately changed to gray. Red became brown and then dark gray, while yellow changed to light gray. On prolonged fixation on a black object, such as the center of a black cross, the part which was in the right and lower field of vision

TABLE 2.—*Fluctuation in Perception of Image from Right Lower Field of Vision with Patient Fixating an Eye in a Mirror Under Conditions Indicated in Columns A to D* *

	A: Binocular Test; Red Pencil on Right Cheek		B: Right Uniocular Test; Red Pencil on Right Cheek		C: Right Uniocular Test; Red Pencil on Right Cheek and Two Yellow Pencils on Left		D: Binocular Test with Simultaneous Stimulation; Right Red Pencil, Left Two Yellow Pencils	
	Time	Duration	Time	Duration	Time	Duration	Time	Duration
Clear	9	4	3	5	..	..	..	..
Blurred	12	22	8	8	3	4	7	9
Clear	35	7	16	6	7	5	16	6
Blurred	42	11	22	9	12	9	22	4
Clear	53	7	31	7	21	4	26	4
Blurred	60	15	38	27	25	16	30	4
Clear	75	31	65	12	41	11	34	4
Blurred	106	24	77	21	52	19	38	7
Clear	130	34	98	11	71	4	45	13
Blurred	164	..	109	8	75	7	58	11
Clear	..	..	117	17	82	11	69	11
Blurred	..	..	134	9	93	..	80	1
Clear	..	..	143	7	..	..	81	8
Blurred	..	..	150	11	..	..	89	8
Clear	..	..	161	..	..	..	97	9
Blurred	..	..	..	..	..	..	106	..

* The conditions indicated in columns A to D are similar to the conditions of the tests shown in table 1. Here, time and duration of clearness or blurring of image are expressed in seconds.

The patient volunteered the information that the image seemed to change faster as the test continued. The blurred image seemed to last longer than the clear image, but this phenomenon was variable. The image was much clearer when it was near the center.

Special Visual Tests.—Perception of Form and Contour: These functions were normal. Localization in space, ability to fuse images and stereoscopic vision were also intact. When the patient was asked to scrutinize at the Schröder staircase illusion,[8] he could see each figure in reversible perspective. As he continued to fixate on the staircase with one or both eyes, the figure continued to reverse itself at a speed similar to the fluctuation rate observed for the right field of vision and as recorded in table 2.

Visual Imagery and Memory: These functions were intact, although at times the patient could not recall the color of tea and of certain animals.

After-Imagery: Uniocular after-imagery tests disclosed normal responses. When examined separately, appeared lighter than black and tended to become gray. Again, while he was fixating on a white cross, the part in the right and lower field became darker than white and approached a gray. Thus, all colors tended to fade and ultimately to change to gray. At times the right horizontal bar of the cross disappeared entirely, and the resultant image was not recognized as a cross. In this sense the gestalt of the exposed object was altered, even though one-half the cross was located in the normal field. All the visual phenomena noted in the affected fields of vision showed notable fluctuation in perception of the form and color of the image.

Displacement of Image: On his figuring columns of numbers, the patient tended to look at the rows to his left. Thus, on adding upward, he noted that the numbers in the upper part of the 10's column were displaced by the adjacent numbers in the 100's column, and then by those in the 1,000's column. On other occasions he noted that after he finished writing a line the first few words were displaced to the right and down, so that the line of words appeared crooked. These displacements appeared to be types of spatial

8. Woodworth, R. S.: Experimental Psychology, New York, Henry Holt & Company, Inc., 1938, p. 696.

disorientation. There was no ring scotoma or diplopia in the homonymous fields, as suggested by Goldstein.[9]

Opticomotor Nystagmus: This phenomenon, elicited by the patient's staring at a revolving vertically striped drum, was present bilaterally, but the quick component was more pronounced to his left.[10]

Ocular Dominance: Alinement and other methods showed that the patient was right eyed.

Muscle Balance: The Maddox rod test showed a 1 degree of esophoria and 0.5 degree of right hyperphoria for distance; 4 degrees of exophoria and 0.5 degree right hyperphoria for near point.

Psychologic Examinations.[11]—Three months after his injury the following features were noted: 1. Indications of an average pretraumatic intellectual level, inferred from average performances in the vocabulary and information tests. 2. Defective performances on retention tests involving speech as the motor response and symbolic material as the content to be retained (digit span and Wells-Ruesch object memory test). However, the performance was adequate on a retention test involving drawing as the motor response and nonsymbolic material as the content to be retained (Benton visual retention test). 3. Adequate abstract reasoning ability in a nonlanguage test (Weigl test). 4. Inferior performance on a test of visual analysis and synthesis (Kohs block designs test). 5. Small number of fairly accurate responses, with failure to interpret two plates, in the Rorschach performance. Five of the ten responses were of the "popular" variety. There were no color responses, but one human movement response was given. The total pattern was similar to the constricted performances described by Harrower-Erickson[11a] for a patient with cerebral tumor.

Psychologic reexamination seven months after the patient's injury showed the following features: (*a*) persistence of defective performance on the digit span test, moderate improvement in the Wells-Ruesch object memory test, which performance, however, was still below the average level, and adequate performance on an alternative form of the Benton visual retention test; (*b*) notable improvement in performance of the Kohs block designs test the patient now performing on a superior level and indicating considerable restoration of visual and analytic-synthetic capacity, and (*c*) no essential change in the Rorschach performance, the same picture of constriction being shown.

COMMENT

Since the injury the patient has shown progressive restitution of visual function. The first sign of recovery was the recession of the right homonymous hemianopsia for motion, color and form. This occurred from the center toward the periphery, and the rate of recovery has been slightly more rapid in the upper quadrants. As these retrograde changes took place other visual disturbances, which are not recognized with ordinary tests, became apparent. The patient sensed the disturbances while reading or looking at motion pictures, and it was these complaints which prompted us to investigate the visual functions in great detail. Although routine perimetric examination seemed to indicate preservation of vision in each field, the simultaneous exposure of objects on the two sides of a fixation point caused the image perceived from the right field to become extinct. Later the extinction phenomenon was replaced by obscuration and still later, by blurring or dulling of the image. These phenomena have been more apparent in the right homonymous inferior quadrants. The image in the right field of vision appeared to fluctuate in clearness of form and intensity of color.

The phenomena of visual extinction, obscuration and dulling seem to be unusual, since they have rarely been observed or reported. This may be due to the fact that few examiners search for these defects, and, as previously noted, the usual neurologic tests will not disclose them. Poppelreuter[1] and others noted one of these phenomena, namely, that of extinction, and explained it on the basis of disturbance in visual attention. The act of perceiving simultaneously exposed objects in zones equidistant from a fixation point requires the normal person to concentrate on three different foci, and his attention must necessarily be divided. Under pathologic conditions a disturbance in the attention mechanism in homonymous fields of vision may occur. Thus, Poppelreuter[1] found that only one of two figures concomitantly exposed on each side of a fixation point could be seen by the patient. However, when the "active attention" of the patient was directed toward the affected field, the patient could see both figures simultaneously. Poppelreuter[1] did not state whether or not the latter observation was a consistent one in his cases. In our case the image in the affected field fluctuated. There were alternate extinction and blurring during the "double exposure" testing. At times it seemed as though the patient could see the object if he "concentrated," but this appeared to be due to a "fluctuation" mechanism which is normally present,[8] and not to an increase or a decrease in attention.

It is probable that weakness of attention is one factor in the elicitation of the extinction phenomenon. Newhall,[12] in controlled experiments,

9. Goldstein, K.: Ueber monokuläre Doppelbilder. Ihre Entstehung und Bedeutung für die Theorie von der Funktion des Nervensystems, Jahrb. f. Psychiat. u. Neurol. **51**:16-38, 1934; Aftereffects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942.

10. Strauss, H.: Ueber die hirnlokalisatorische Bedeutung des einseitigen Ausfalls des optikinetischen Nystagmus und der hemianopischen Aufmerksamkeitsschwäche, Ztschr. f. d. ges. Neurol. u. Psychiat. **143**:427-435, 1933.

11. Performed by Lieutenant Commander A. L. Benton, H(V)S, U.S.N.R.

11a. Harrower-Erickson, M. R.: Personality Changes Accompanying Cerebral Lesions (Rorschach Studies of Patients with Cerebral Tumor), Arch. Neurol. & Psychiat. **43**:859-890 (March) 1940.

12. Newhall, S. M.: Effects of Attention on the Intensity of Cutaneous Presence and on Visual Brightness, Arch. Psychol. (no. 61) **9**:1-75, 1923.

found that the closer the attention the better discrimination there is between faint stimuli and no visual stimulus. Still, it does not appear that the attention mechanism alone would account for the visual extinction, obscuration or color-dulling phenomena. Goldstein [13] also expressed the opinion that these phenomena are not due to lack of attention. He proposed the theory that the cause of these different reactions may be due to "lability of threshold" in a damaged cortex, which needs more energy than the normal. The nerve energy in the organism is a constant, and the normal cortex, he stated, tends to use the available energy to such an extent that the remaining energy is not sufficient to stimulate the diseased cortex to effect a performance. Granted the correctness of this theory, one must, however, take into consideration the rivalry and dominance mechanisms in explaining the extinction and associated phenomena. Rivalry and dominance are normal psychologic processes and can be detected only with special tests. Sherrington [14] demonstrated the existence of rivalry between the images perceived by the two eyes, or half-retinas. Breese [15] and others showed that stimuli arising from the two fields of vision are in constant competition with each other. Light intensity, presence of figures or movements of the object exposed influence the subject's ability to visualize the images in the two fields equally: (*a*) The brighter the exposed field, the more visible it is 60 per cent of the time; (*b*) a field containing lines prevails over a plain field as much as 70 per cent of the time, and (*c*) when both fields contain figures and the one figure in one field is made to move, it remains in sight more than half the time.

Rivalry, dominance and attention mechanisms are normal psychologic processes which operate at all times and are a function of the cortex. The visuosensory cortices are in competition with each other and are in equilibrium when at rest. If one cortex is diseased, as it was in our patient, the visual stimuli coming to that side are not as well integrated as those coming to the normal side. The affected cortex does not possess the nerve energy as does the normal cortex, or the capacity to use it when the incoming stimuli are increased. Consequently, there must be a difference in perception, and this difference is made more conspicuous by the rivalry and dominance mechanism. Hence, when there are no new or strong stimuli in the normal field of vision, there is no appreciable decrease in perception of an object held in the pathologic field. The available "energy" is sufficient for the diseased cortex to function, and there is little competition between the two sides. However, if stimuli are thrown into the intact field, the rivalry mechanism becomes apparent. The function of the defective cortex is dominated by the normal part of the brain, and there results a relative decrease in acuity and light intensity in the affected field of vision, leading to the phenomena of dulling and obscuration. The rivalry and consequent dominance of the normal over the pathologic side may be so pronounced as to cause complete extinction of the form, color and movement of the image perceived from the affected field. It has been found that the more the normal half is stimulated, the less the affected half perceives.

Such competition may under certain conditions interfere with the patient's proper visual perception. It is known that the perceptual consciousness of an object is the effect of integrated stimuli in which the total stimulus pattern is related to the total reaction pattern through a unified neural mechanism. If the rivalry between sensations arising from the opposite lateral fields of vision becomes pronounced, as in reading or looking at motion pictures, the images coming from the affected fields of vision blur, and the patient's total visual perception becomes impaired. Similar competitive mechanisms have been noted between the cutaneous sensations on the two sides of the body in the patient described in this report, in patients with lesions of the parietal cortex (personal observations) and between certain reflexes, as demonstrated by Sherrington.[16]

SUMMARY

In a patient with a gunshot wound of the left occipitoparietal cortex, various psychologic mechanisms became apparent during the advanced stages of restitution of visual function from right homonymous hemianopsia. Visual stimuli originating in the normal homonymous field of vision tended to suppress or obscure the image originating simultaneously in the opposite, affected, field of vision. The more stimulation there was in the normal field, the less the patient saw in the pathologic field of vision. The affected field showed fluctuation of sensation. Rivalry, dominance and attention mechanisms are considered as explanatory principles.

13. Goldstein, K., in discussion on Phenomenon Visual Extinction in Homonymous Fields, Tr. Am. Neurol. A., 1944, to be published; personal communications to the authors.

14. Sherrington, C.: On Binocular Flicker and the Correlation of Activity of Corresponding Retinal Points, Brit. J. Psychol. **1**:26, 1904.

15. Breese, B. B.: Binocular Rivalry, Psychol. Rev. **16**:410-415, 1909.

16. Sherrington, C.: Intergrative Action of the Nervous System, New Haven, Conn., Yale University Press, 1906.

MENTAL SYMPTOMS FOLLOWING HEAD INJURY

A STATISTICAL ANALYSIS OF TWO HUNDRED CASES

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PRESENT INVESTIGATION

METHOD

From a total of 430 patients with head injuries admitted to the Boston City Hospital between July 1942 and September 1944 a series of 200 was selected for study. Two hundred and thirty patients were eliminated because no adequate follow-up observations could be obtained, because the patients were under 15 or over 55 years of age or because they were vagrants or chronic alcohol addicts. The patients had all sustained recent injuries; they were seen on admission to the hospital, were closely followed during their stay in the hospital and were observed at intervals of two to three months thereafter. The present report deals with their post-traumatic mental symptoms and the relation of these symptoms to the other fields of investigation.

The group of examiners consisted of neurologists, psychiatrists, a psychometrist, an electroencephalographer and a social worker.

MATERIAL

Age, Sex and National Stock.—The age distribution of the 200 patients was as follows:

Age, Years	No. of Patients
15-19	36
20-29	48
30-39	42
40-49	51
50-55	23

There were 125 males and 75 females, and the following national stocks were represented:

Irish	77
English	29
Latin	21
Negro	13
Slavic	12
Semitic	12
German or Scandinavian	10
Other racial stocks	26

Occupation.—Skilled or semiskilled

workers	96
Domestics or housewives	39
Students	20
Policemen, firemen, etc.	13
Common laborers	11
Other workers	21

Alcoholism.—For 143 patients there was no evidence of alcohol on admission; 53 had ingested alcohol but were not intoxicated, and 4 were intoxicated.

Manner of Injury.—The accidents could be classified as follows:

Traffic accidents	91
Industrial accidents	24
Fighting or robbery	24
Falls on street	16
Domestic accidents	15
Recreational accidents	12
Other types	18

Coma and Disorientation.—Twenty patients had no period of coma; 90 patients were comatose or semicomatose for less than ten minutes; 42 patients, for less than thirty minutes; 20 patients, for thirty to sixty minutes; 17 patients, for up to six hours; 5 patients, for six to twenty-four hours, and 4 patients over twenty-four hours. For 2 patients the duration of coma was uncertain but brief. One hundred seventy-three patients were disoriented for less than twelve hours; 4 patients, for twelve to twenty-four hours; 12 patients from one to seven days, and 11 patients, over seven days.

In accordance with general usage, the period of coma was judged by the absence of response to stimulation. The period of disorientation was usually recorded by disorientation in time. The duration of post-traumatic amnesia and retrograde amnesia was recorded on the patient's follow-up visit to the clinic when the amnesia had reached its stable minimum. The presence or absence of complicating factors, such as litigation or occupational and financial difficulties, was recorded without reference to their possible bearing on the development of post-traumatic mental complications.

Type of Injury.—Seventy-five patients had minor abrasions or hematoma of the scalp; 75 patients, laceration of the scalp and 6 patients, laceration with compound fracture. Thirty-five

From the Neurological Unit of the Boston City Hospital, and the Department of Neurology, Harvard Medical School.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College.

patients had injuries to the limbs, and 24 patients had other or multiple injuries, in addition to the head injury. Evidence of fracture of the skull was present in 34 patients. Nine had cranial operations other than scalp suture, and 13 had operations of other types. One patient had both cranial and other operations.

The type of head injury represented by this material is therefore representative of those encountered among patients admitted to any general hospital and may be categorized predominantly as "closed head injury."

Length of Follow-Up Observation.—One patient was observed one month; 1 patient, two months; 48 patients, four to six months; 107 patients, six to nine months; 18 patients, nine to twelve months, and 25 patients over one year.

STATISTICAL EVALUATION OF MATERIAL

In evaluation of post-traumatic mental symptoms the mental condition immediately following an injury must be distinguished from that during the later part of the course. Any person might be impressed by a violent injury which may have brought him to the verge of death and may have resulted in injury and death to others and in loss of property to a varying degree. Such an emotional reaction might be expected normally to be at its height immediately after the injury, after which it would steadily subside. Outwardly, however, 133 of the 200 patients (67 per cent) gave an impression of calmness and cooperativeness; 20 were apathetic; 7 were excited; 16 had a severe emotional reaction, and 24 were confused.

Post-traumatic mental symptoms may be related to structural lesions or may be psychogenic. Some psychologic phenomena are known to be caused by structural lesions. For instance, this is the case with patients suffering from dysphasia or confabulations. The purpose of this study was to evaluate mental symptoms according to their correlation with all the other physical and mental factors of the head injury. The analysis is therefore of the patient's symptoms (complaints) in order that all possible objectivity may be maintained. Early in our experience my colleagues and I found that these complaints tended to fall into a limited number of categories, symptoms of anxiety, nervousness and fatigue emerging as leading factors, especially in the production of disability. The incidence of these mental symptoms during convalescence is given in table 1. It will be noted that by far the largest group of patients (48 of 70) fell into the category of those showing anxiety and fears, symptoms which were present more than twice as often as all the others combined.

It would be a misunderstanding to conclude from table 1 that the symptoms of fatigue and nervousness were present in only 7 and 4 patients respectively. Fatigue and nervousness were present, in addition to fears and anxiety, in practically every patient who presented the latter symptoms. Patients whose "predominant mental symptom" was fatigue or nervousness were persons in whom no anxiety reactions were present. On the other hand, the symptoms of the acute post-traumatic anxiety neuroses included syndromes such as acoustic hypersensitivity, periodic irritability, fatigue, disturbances in sleep and anxiety dreams, anxiety being the primary and predominant feature of these secondary character changes. There was no case of hysteria among our patients.

The symptoms of headache and dizziness are not taken into account in our psychiatric diagnoses.

TABLE 1.—*Predominating Post-Traumatic Mental Symptoms*

	No. of Patients
None	130
Fatigue	7
Nervousness; inability to concentrate	4
Fears; anxieties; panics	48
Depression; apathy	1
Hypochondriasis	2
Obsessive-compulsive neurosis	1
Hysteria	0
Personality change only	6
Hypomania; euphoria	1
Total	200

PRETRAUMATIC FACTORS ASSOCIATED WITH HIGH AND LOW INCIDENCES OF POST-TRAUMATIC MENTAL SYMPTOMS (TABLES 2 AND 3)

Age.—Of the patients of the oldest group (50 to 55 years), 51 per cent manifested mental symptoms, as compared with an average of 31 per cent of all patients and of only 15 per cent of the youngest group (15 to 19 years). No notable difference in occurrence of post-traumatic mental symptoms could be found in the intervening age groups.

Marital Status and Sex.—More women had mental complications than men, with a negligible difference between the incidence for married women and that for single women. However, fewer single than married men had mental complications.

Anxiety symptoms were present four times as often as all other mental symptoms combined in men, whereas in women anxiety symptoms were less than three times as frequent as fatigue and nervousness combined.

National Stock.—In 50 per cent of the patients of Latin and Slavic stock mental com-

plications developed, whereas only 17 and 21 per cent of the African and Irish patients respectively presented psychologic difficulties. There was a fairly even distribution among the other racial stocks, some of which, however, presented numbers too small for statistical evaluation.

Type of Accident.—By far the highest incidence of mental complications was found among

TABLE 2.—*Miscellaneous Pretraumatic Factor Associated with Low Incidence of Post-Traumatic Mental Symptoms*

	No. of Patients	Post-traumatic Mental Symptoms, %	No Post-traumatic Mental Symptoms, %	Personality Change Only, %
All patients	200	31.5	65.0	3.5
Age, yr.				
15-19	36	15	85	
Sex and marital status				
Male; single	45	14	86	
National stock				
African	13	17	83	
Irish	77	21	79	
Alcoholism on admission				
Intoxicated, or previous alcoholic ingestion	57	12	88	
Type of accident				
Recreational	12	8	92	
Domestic	15	13	87	

TABLE 3.—*Miscellaneous Pretraumatic Factors Associated with High Incidence of Post-Traumatic Mental Symptoms*

	No. of Patients	Post-traumatic Mental Symptoms, %	No Post-traumatic Mental Symptoms, %	Personality Change Only, %
All patients	200	31.5	65.0	3.5
Age, yr.				
50-55	23	51	49	
Sex and marital status				
Female; single and widowed	40	45	55	
National stock				
Slavic and Latin	38	50	50	
Occupation				
Policemen and firemen	13	58	42	
Alcoholism on admission				
No evidence of ingestion of alcohol	143	39	61	
Type of accident				
Industrial	24	55	45	
Manner of injury				
Struck by vehicle	45	50	50	
Pretraumatic psychiatric evaluation				
Preexisting anxiety; hypochondriasis; depression	21	57	43	

the patients who had suffered industrial accidents. Only 1 of the patients who had sustained their head injuries during recreational activities and only 2 of the patients who had suffered injuries during domestic activities presented mental symptoms.

Occupation.—The highest incidence of post-traumatic mental symptoms was observed among policemen and firemen. Next to the frequency for this group was the incidence for the common laborers. The large group of patients classified as skilled and semiskilled workers presented an average incidence of mental complications.

Alcoholism on Admission.—In only a few patients with a history of ingestion of alcohol previous to injury did post-traumatic mental difficulties develop.

Psychiatric Family History.—The incidence of post-traumatic mental complications was highest among the patients with psychotic family members. On the other hand, it was low among the patients who had alcohol addicts and other types of psychopaths in their families. However, the numbers are too small to be of statistical significance.

Pretraumatic Psychiatric Evaluation.—The highest incidence of mental symptoms prevailed among patients with preexisting symptoms of anxiety, hypochondriasis and depressive neuroses. Next to this group came patients with preexisting general nervousness, in half of whom mental complications developed. Not all types of patients with preexisting neuroses reacted in this way, however. For instance, of the 5 patients with previous hysterial episodes, only 1 manifested psychiatric difficulties.

POST-TRAUMATIC FACTORS (TABLES 4 AND 5)

The difference between the incidence of post-traumatic mental symptoms for patients who sustained injuries in addition to those of the head and the incidence for patients who had head injuries only was negligible. The largest percentage of post-traumatic mental symptoms was found, however, among patients with additional injuries to their legs, whereas injuries to the face, chest, abdomen and arms each carried a comparatively low incidence.

Duration of Stay in Hospital.—Fewer patients who remained in the hospital for from four to seven days presented mental symptoms than did the patients who remained in the hospital for longer than fourteen days. The incidence of mental symptoms in patients who stayed less than four days was within the average range.

Post-Traumatic Headache and Dizziness.—The incidence of post-traumatic mental symptoms was high in patients who suffered from post-traumatic headache or dizziness. The incidence was highest for patients whose headache and/or dizziness lasted more than two months, whereas there was an average incidence of mental complications among patients for whom the duration of headache and/or dizziness was less than two months.

Associated Symptoms Immediately Following Injury.—Many patients who had both headaches and dizziness immediately after injury presented psychiatric complications, while patients who had none of these symptoms while in the hospital had a low incidence of mental symptoms.

TABLE 4.—*Miscellaneous Post-Traumatic Factors Associated with Low Incidence of Post-Traumatic Mental Symptoms*

	No. of Patients	Post-traumatic Mental Symptoms, %	No Post-traumatic Mental Symptoms, %	Personality Change Only, %
All patients	200	31.5	65.0	3.5
Duration of coma				
No coma or dazed state.	20	15	85	
Duration to recovery of complete orientation				
No measurable disorientation	18	16	84	
Post-traumatic amnesia				
No post-traumatic amnesia	17	12	88	
Associated symptoms immediately following injury				
None	63	19	81	
Signs of injury				
Minor abrasions of face or scalp	31	19	81	
Injuries other than those involving head				
Injury to face, chest, abdomen or back	35	20	80	
Injury to arm	24	21	79	
Duration of stay in hospital				
4-7 days	33	21	79	
Post-traumatic headache				
No headache	119	13	87	
Headache localized to side other than injury	15	20	80	
Post-traumatic dizziness				
No dizziness	127	15	85	
Post-traumatic dreams				
No dreams	75	5	95	
Measured post-traumatic intelligence				
Above normal intelligence	21	24	76	
Complicating factors, regardless of influence on post-traumatic course				
No complicating factors	72	6	94	

RESULTS OF POST-TRAUMATIC LABORATORY AND PHYSICAL EXAMINATIONS

Cerebrospinal Fluid.—Of the 7 patients with personality changes, 6 had a bloody spinal fluid, with a pressure above 200 mm. On the other hand, no correlation was found between the pressure and the content of blood of the spinal fluid and the development of the remaining psychogenic mental symptoms.

Blood Pressure During Later Part of Hospitalization or on Follow-Up Observation.—No correlation between the blood pressure and the incidence of post-traumatic mental symptoms was apparent.

Electroencephalographic Changes.—No correlation existed between the character or the severity of the electroencephalographic abnormality and the incidence or duration of post-traumatic mental symptoms.

Roentgenographic Changes.—Only 13 patients in the series gave roentgenographic evidence of fracture of the skull, and among these persons the incidence of post-traumatic mental symptoms was only slightly above the average.

Duration of Coma, Disorientation and Amnesia Following Head Injury.—Coma, disorientation and post-traumatic amnesia are all evidences of the initial disturbance of consciousness, and hence the immediate traumatic disorder of cerebral function. Whereas the frequency of mental symptoms did not vary to any considerable extent with the duration of coma, there was a low incidence of psychiatric complications among patients in whom no complete loss of consciousness had occurred. It was also noted that patients without measurable disorientation had a low incidence of mental symptoms. Variations in duration of disorientation, when present, had no significant influence on the frequency of mental symptoms. Likewise, only a small percentage of

TABLE 5.—*Miscellaneous Post-Traumatic Factors Associated with High Incidence of Post-Traumatic Mental Symptoms*

	No. of Patients	Post-traumatic Mental Symptoms, %	No Post-traumatic Mental Symptoms, %	Personality Change Only, %
All patients	200	31.5	65.0	3.5
Duration of coma				
More than 30 minutes	42	39	61	
Duration to recovery of complete orientation				
More than 12 hours	27	41	59	
Post-traumatic amnesia				
More than 2 days	22	41	59	
Associated symptoms immediately following injury				
Headache and dizziness	76	48	52	
Signs of injury				
Laceration of scalp	75	42	58	
Injuries other than those involving head				
Injury to lower limbs	17	48	52	
Immediate post-traumatic mental state				
Normal but severe emotional reaction	16	59	41	
Duration of stay in hospital				
More than 14 days	30	47	53	
Post-traumatic headache				
Any type	81	64	36	
Duration of headache				
More than 2 months	63	75	25	
Post-traumatic dizziness				
Any type	68	67	33	
Duration of dizziness				
More than 2 months	46	78	22	
Dreams				
Post-traumatic anxiety dreams	29	100	0	
Complicating factors, regardless of influence on post-traumatic course				
More than one factor	14	93	7	
Occupational difficulties.	11	73	27	
Pending litigation	34	59	41	

patients who had no post-traumatic amnesia presented mental complications, and there was no significant correlation between duration of post-traumatic amnesia, when present, and incidence of psychiatric symptoms.

Duration of Retrograde Amnesia.—Except for 8 patients, the retrograde amnesia was either of very short duration, not beyond a few minutes, or not present. Of the 8 patients, 4 had been intoxicated at the time of injury, and the remaining 4 patients suffered serious injuries, as expressed by fractures of the skull and long-lasting post-traumatic amnesia. It is interesting that in only 1 of the 8 patients with a retrograde amnesia of more than one hour did psychogenic symptoms develop. This patient was an alcoholic psychopath with a great many pretraumatic symptoms of anxiety whose preexisting psychiatric condition was slightly worse for three months after injury.

Time of Onset of Mental Symptoms as Compared with Time of Onset of Headache and Dizziness.—The onset of post-traumatic mental symptoms as compared with that of headache was later on an average. Of the 59 patients whose mental symptoms lasted longer than two months, the majority had an onset of mental complications during the first to the eighth week after leaving the hospital. On the other hand, of the 62 patients with post-traumatic headaches lasting more than six months, the great majority (41 patients, or 82 per cent) had headaches during hospitalization. Likewise, in the majority of patients (35, or 76 per cent) with post-traumatic dizziness of more than two months' duration the onset was during hospitalization.

Influence of Environmental Complications on Post-Traumatic Psychiatric Difficulties.—The presence or absence of environmental factors in convalescence was recorded regardless of their significance in the opinion of the psychiatrist. Problems in relation to litigation and compensation and occupation had a significant correlation with the development of post-traumatic mental symptoms, whereas social or sexual difficulties, as well as coexisting physical disease, influenced the psychiatric condition more seldom. In table 6 the data on these factors are presented in detail.

Closer investigation showed the influence of such complicating factors on all but 4 of the 63 patients with post-traumatic mental complications. It is interesting, however, to note that in only about one half to one third of all patients for whom complicating factors were noted did such a factor become associated with post-traumatic psychiatric difficulties. For instance, whereas litigation alone formed a complicating factor in the cases of 34 patients, it was correlated with mental difficulties in only 20 patients. With each patient it was not the complicating factor in itself, but the manner in which the patient reacted to the complication, before as well as after the injury, that was essential for the development or absence of post-traumatic mental complications.

TABLE 6.—*Complicating Factors Appearing in the Post-Traumatic Psychiatric Course* *

	No. of Patients	Post-traumatic Mental Symptoms, %	No Post-traumatic Mental Symptoms, %
None	72	6	94
Litigation, compensation	34	59	41
Diseases other than mental	28	32	68
Domestic and family troubles	18	33	67
More than one, including litigation	14	93	7
Occupational difficulties	11	73	27
Other financial problems	8	13	87

* Personality changes only were not included among the post-traumatic mental disorders.

COMMENT

Age.—The preponderance of mental complications in the older age groups is probably related to more frequent problems of occupational and financial adjustment.

Marital Status and Sex.—Occupational and financial problems, which are more pressing in the married state, probably favored the high incidence of mental difficulties among married males.

Type of Accident.—Evidently the compensation problem which is connected with industrial accidents, accidents which are followed most frequently by mental symptoms, is a strong contributing factor in the development of mental difficulties.

Occupation.—The high incidence of mental complications among policemen and firemen can probably be attributed to their attitude toward the hazards of their occupation, as occupational factors had no influence on the students, only a few of whom showed mental symptoms.

Effect of Alcoholic Intoxication on Admission.—The low incidence of post-traumatic mental symptoms in patients with a history of ingestion of alcohol previous to injury can be compared with the results of the investigation of the incidence of post-traumatic neuroses in victims of the Cocoanut Grove disaster.[1] Of the victims who had a long-lasting amnesia which blotted out parts or all of the terrifying events, only 19 per cent had a post-traumatic neurosis,

1. Adler, A.: Neuropsychiatric Complications in Victims of Boston's Cocoanut Grove Disaster, J. A. M. A. **123**:1098-1101 (Dec. 25) 1943.

whereas the incidence was 75 per cent for patients who had amnesia for less than five minutes or no amnesia. It can be assumed that the psychologic impression of the injury is less vigorous if the patient is under the influence of alcohol. In deeply intoxicated patients there is of course no memory of the injury at all. Actually, about one half of all persons with head injuries who had retrograde amnesias of longer than five minutes had been intoxicated at the time of injury.

Duration of Stay in Hospital.—Evidently prolonged stay in the hospital decreases the patient's chances to adjust probably because his thoughts become increasingly centered around his injury, which impresses him as more serious when his stay in the hospital is prolonged. On the other hand, an initial protective environment provided by a few days' hospitalization and reassurance from the physicians seems preferable to the regimen of having the patient leave the hospital within the first few days, so that he is thrown on his own resources in his readjustment.

Duration of Coma, Disorientation and Amnesia.—The low incidence of post-traumatic mental symptoms in patients who had no coma or disorientation might be explained by assuming that these patients felt that nothing serious had happened to them, an attitude which is helpful for future readjustment.

DESCRIPTION OF POST-TRAUMATIC PSYCHIATRIC SYNDROMES

The patients with mental symptoms could be divided into two groups: patients who had not shown psychiatric abnormalities previous to injury and patients whose pretraumatic psychiatric condition had grown worse through accentuation of previously existing symptoms or through the addition of new mental symptoms to those already present.

TABLE 7.—*Relation of Pretraumatic to Post-Traumatic Mental Symptoms* *

	Total No.	No. with Post-Traumatic Mental Symptoms
Patients with no abnormality in the pretraumatic personality	89	26 (29%)
Normal pretraumatic personality, but minor variants	31	9 (29%)
Patients with abnormal pretraumatic personality	71	26 (37%)

* In 9 patients the pretraumatic personality could not be evaluated because data were insufficient.

Table 7 reveals that only slightly fewer patients of previously normal personality (29 per cent) presented post-traumatic symptoms than did patients with pretraumatic psychiatric difficulties (37 per cent).

Of the 26 patients with normal pretraumatic personalities who had mental complications, symptoms of anxiety were present in 23, an incidence eight times that of all the other symptoms combined. On the other hand, in patients with previous psychiatric difficulties anxiety developed only two and a half times as often as all the other symptoms combined. It can therefore be stated that, particularly in previously normal patients, the type of psychiatric difficulty was predominantly the anxiety neurosis. The psychiatric syndrome in patients with pretraumatic mental difficulties varied to some extent through modification of previous liabilities.

POST-TRAUMATIC ANXIETY STATES

McCurdy [2] gave a thorough description of a type of acute post-traumatic anxiety neurosis which he named "anxiety state," a designation applied to this condition ever since. Roussy and Lhermitte [3] and Kardiner [4] described this condition among the neuroses of World War I. Literature concerning this subject gathered from observations made in the present war is growing rapidly (Blain,[5] Brosin,[6] Garmany,[7] Henderson and Moore,[8] Kubie,[9] Raines and Kolb,[10] Sagebill and Bird,[11] Symonds,[12] and Torrie.[13]) There is a striking uniformity of symptoms in

2. McCurdy, J. T.: War Neuroses, London, Cambridge University Press, 1918.

3. Roussy, G., and Lhermitte, J.: The Psychoneuroses of War, translated by W. B. Christopherson, London, University Press, 1918; Paris, Masson & Cie, 1918.

4. Kardiner, A.: The Traumatic Neuroses of War. Psychosomatic Medicine, Monograph II-III, New York, Paul B. Hoeber, Inc., 1941.

5. Blain, D.: Personal and Morale Factors in the Etiology and Prevention of Traumatic War Neurosis in Merchant Seaman, Am. J. Psychiat. **100**:131-135 (July) 1943.

6. Brosin, H. W.: Panic States and Their Treatment, Am. J. Psychiat. **100**:54-61 (July) 1943.

7. Garmany, G.: Reactive Anxiety and Its Treatment, Lancet **1**:7-9 (Jan. 1) 1944.

8. Henderson, J. L., and Moore, M.: The Psychoneuroses of War, New England J. Med. **230**:275-278 (March 9) 1944.

9. Kubie, L. S.: Manual of Emergency Treatment for Acute War Neuroses, War Med. **4**:582-598 (Dec.) 1943.

10. Raines, G. N., and Kolb, L. C.: Combat Fatigue and War Neurosis, U. S. Nav. M. Bull. **41**:1299-1309 (Sept.) 1943.

11. Sagebill, J. L., and Bird, L. C.: A Study of Psychiatric Casualties Received at the U. S. Naval Base Hospital—from the Solomon Islands Battle Area, U. S. Nav. M. Bull. **41**:1927-1937 (Nov.) 1943.

12. Symonds, C. P.: Anxiety Neuroses in Combatants, Lancet **2**:785-789 (Dec. 25) 1943.

13. Torrie, A.: Psychosomatic Casualties, Lancet **1**:139-143 (Jan. 29) 1944.

patients suffering from this condition. In the following discussion some features observed in our patients with head injuries are emphasized.

It was usual to find that patients were conscious that their fears and panics were related to the accident as such. For instance, persons who had suffered traffic accidents felt unable to cross a street or began to shake and had to cling to some one to lead them over. People who had been drivers of cars when the accident occurred were unable to drive again, and some had states of panic, with trembling and perspiring on the mere thought of doing so again. Firemen who had sustained their accidents during work trembled at the mere thought of going back to work, climbing ladders and fighting fires again. The sound of passing fire sirens threw them into panic states. Anxiety regarding the condition of the head was expressed by less than half these patients. Such persons expressed fear that they might become insane or paralyzed, that pressure on the brain might develop, that something in the head might be irreparably broken or that the memory might be permanently impaired. Reassurance from the physician alleviated, but did not cure, their anxiety state.

POST-TRAUMATIC NIGHTMARES

The anxiety state was further characterized by the occurrence of nightmares. Of 70 patients with mental symptoms, 39 suffered from post-traumatic anxiety dreams, 11 of these having had nightmares previous to injury also. Of the remaining 31 patients with mental symptoms, 18 had no dreams, and no information concerning dreams was obtained from the other 13. Of the 18 patients who had mental symptoms but no anxiety dreams, 7 had no neurosis but presented a personality change only, evidently related to structural changes of the brain. Two other patients had depressed emotions related to accompanying injuries of long duration. In 7 of the remaining 9 patients, the post-traumatic condition was a mere exacerbation of previously existing psychiatric liabilities. Only 2 patients with normal pretraumatic personalities had an anxiety condition which had developed after injury and which was not accompanied by anxiety dreams. One of these, a young woman, dreamed of seeing her dead father, although she had never dreamed of him before. The case was that of a clearcut "compensation neurosis," and the father's death had been of decisive influence on the patient's financial condition. This patient is still in the midst of litigation procedures for a large sum, although her injury was comparatively small. She takes an active and determined interest in the procedures, with all her anxieties centered around the compensation. The second patient, who, after his accident, was afraid of returning to his former occupation, which he had previously disliked because of associated danger, dreamed about his return to another, preferred type of work. He actually never returned to his former occupation and evidently had made up his mind not to do so rather soon, thus evading anxiety.

The patients regularly woke from the anxiety dreams with a start, trembling and perspiring. Only 4 of the 39 patients with post-traumatic nightmares had these dreams during the first few nights following injury. The dreams represented a reaction to the frightening experience, and thus they repeated the accident with hardly any distortion. For instance, a young laborer, who had been pushed by a car for some distance before hitting the pavement, relived the frightening experience in several anxiety dreams during the first few nights following the accident. The nightmares of the remaining 35 patients occurred after an interval during which they had sufficiently recovered to return home, usually during the first or second week at home. This delay indicates their anxiety in relation to their pending obligations, rather than merely a horror connected with the injury itself. Consequently, the dream content was distorted, and was concerned with mutilation and destruction, often with the patient bleeding. This delay is in contrast to the immediate occurrence of nightmares in patients who had gone through some harrowing experience which had dazed them to such an extent that for some time they were unable to deal with it on a conscious level. I [1] observed the immediate appearance of nightmares in 15 of the 25 patients who were subjected to the horrors of a disaster with burns and partial asphyxiation (Cocoanut Grove fire in Boston). These dreams also repeated incidents of the disaster with hardly any distortion of content.

Prolonged physical disability, such as that caused by accompanying injuries, occasionally brought about long delay in appearance of anxiety symptoms and anxiety dreams. For instance, in a patient who had been kept in bed for six months because of a fractured leg anxiety dreams developed only at the end of that time, together with other symptoms of anxiety, which then prevented him from returning to full work.

All 28 patients with post-traumatic anxiety dreams and no such dreams previous to injury also presented other symptoms of anxiety. Cases of this type have been reported by McCurdy,[2]

Kardiner [4] and Schilder [14] in their descriptions of patients suffering from post-traumatic anxiety neuroses.

It is interesting to note that none of the 8 patients with retrograde amnesia lasting more than one hour had anxiety dreams, but the number of patients is too small to justify definite conclusions.

The presence and prolonged duration of headaches and dizziness were noted two to three times as often in patients with post-traumatic nightmares as in the whole group of 200 patients.

ATTITUDE TOWARD EMPLOYMENT

In 8 of the 11 patients in whom occupational difficulties had been noted the attitude toward employment underwent a characteristic change after the injury. They had worked steadily before injury but had been laboring for some time under emotional stress in relation to their occupation, which they resented because of associated danger or monotony or because they felt unduly burdened. After injury this chronic tension developed into an acute exacerbation, which became incapacitating because of associated fears and other mental symptoms. This condition freed them from their obligations to continue their former occupation. The use of this mechanism of "secondary gain" is a part of the neurotic symptom formation, and as such is unconscious. Six of the 8 patients never returned to their former work. Three of them are still incapacitated because of their anxieties in relation to resuming their previous work, and the other 3 patients changed to another type of work. The 2 housewives succeeded in securing the help of their families in their housework after they had been trying unsuccessfully to do this for years prior to the injury. This resentful, dissatisfied attitude of patients toward their work can be found on careful psychiatric exploration immediately after injury, and the development of anxiety neuroses in such patients can be anticipated. At that stage patients with head injury give no evidence of anxiety related to the injury but the great majority exhibit a contemplative mood, actually expressing their intention of returning to work. Their initial physical disability protects them at this time from resuming their responsibilities. Therefore the duration of this "preneurotic interval" varies according to the severity of the physical injury. Roussy and Lhermitte [3] have described this phase, designating it as one of "incubation and contemplation." Final judgment about the patient's mental reaction to the injury can be made only after he is physically fit to return to work. This accounts for the frequent delay in onset of mental symptoms as compared with the time of onset of headaches and dizziness. The longest delay was observed by us in a 53 year old worker whose case has been mentioned in a previous part of this paper because of the occurrence of delayed nightmares. For many years he had had an inner conflict between his dislike of an occupation which he found monotonous and his feeling that it was his duty to stay on the job for the sake of financial security. For the six months following injury, while physically incapacitated because of a complicating fracture of the leg, he declared himself resolved to return to full work as soon as his leg was healed. His mood was pensive, given to meditation over his type of work, but not anxious. When he was faced with the necessity of resuming his occupation, however, typical anxiety states and nightmares developed, a condition which has made it impossible for him to resume full time work, and he is about to make a change in his occupation. This type of neurosis, originating in a conflict between a sense of duty or self respect and the patient's idea of self preservation, may well be designated a "conflict neurosis," as was done by Symonds [12] in a recent paper. He differentiated another type, "fear neurosis," which originates in the experience of frightening events which the patient is unable to balance and which initiate fear reactions. The great majority of neuroses which develop after civilian head injuries are "conflict neuroses," since the actual accident is usually of short duration and devoid of frightening content, and may be totally blotted out by long-lasting retrograde amnesia or preceding consumption of alcohol. In only 4 of our patients was the reaction that of a "fear neurosis." In them there was no delay in onset of anxiety, but they showed pronounced emotional disturbance while in the hospital, and their anxiety dreams occurred during the first nights in the hospital. One was a laborer aged 21 who had been dragged along by a car for a long distance before hitting the pavement. His anxiety neurosis started while in the hospital, and he gave the impression of suffering from a severe fright reaction. Nightmares, during which he relived the frightening experience, tormented him during the nights following the accident and for a few months thereafter.

No attempt was made to prevent the development of a "conflict neurosis" in civilians by early psychotherapy. It appears that if there is evi-

14. Schilder, P.: Neuroses Following Head and Brain Injuries, in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, William Wood & Co., 1940.

dence of conflict in relation to pending obligations the "preneurotic interval" between the injury and full development of the neurosis is the most suitable time for preventive psychiatric measures.

Unless a post-traumatic neurosis developed, no post-traumatic change of attitude toward employment could be noted. Patients who had unsatisfactory work records continued after injury to be failures at work. In particular, it should be stressed that mere dissatisfaction with work does not imply the presence of a conflict, conducive to the development of post-traumatic neurosis. There were several patients who openly disliked their kind of work, for instance, students who hated school and planned to leave and start work, and several adult workmen. But, unlike the potential neurotic patient, they openly strove to bring about a change and often succeeded in doing so without having to resort to the detour of neurotic mechanisms originating from conflicts.

In addition, our 7 patients with personality changes which were evidently caused by damage to the brain did not show any changes of attitude toward employment. These observations suggest the advisability of careful scrutiny of underlying causes before the statement is made that injury to the brain is often associated with change of attitude toward work. To understand such a change, an accompanying statement about the presence or absence of post-traumatic neurosis is mandatory.

OTHER ENVIRONMENTAL COMPLICATIONS

A mechanism similar to that resulting from conflict in relation to occupation could be found in relation to other environmental problems. Problems of litigation and compensation were associated with an unfavorable psychiatric course in 20 of 34 patients who had such problems. All these patients had been harassed by debts and other financial obligations for some time before injury. After injury their interest centered around the problem of compensation, through the solution of which they hoped to be relieved of their previous anxieties.

For instance, 1 patient had been unable to pay dues on her insurance for almost a year prior to her injury. Another patient had been anticipating with anxiety the time when her brother was expected to enter the Army, and by a coincidence this happened a few days after her head injury. Two other patients had been overconscientious and overanxious in obtaining financial security. These were the patients who after injury centered their anxieties about the compensation problem, as though a satisfactory settlement of their claims might present an escape from their previous anxieties.

PSYCHOLOGIC REACTION TO THE INJURY ITSELF IN PATIENTS WHO DID NOT PRESENT POST-TRAUMATIC NEUROSES

The psychologic reaction to the injury itself was studied in detail in 35 patients who had not shown any post-traumatic mental symptoms. Of these, 18 showed no psychologic reaction whatever to the injury. Answers, such as "I never gave it a thought," or "It never bothered me," were given repeatedly. The remaining 17 patients showed a reaction which should not be confused with that of post-traumatic neurosis, since its course and prognosis differ considerably from the latter condition. These patients reported initial concern about either the outcome of their injury or their ability to go through conditions repeating the circumstances of the accident, but they were able to control their thoughts and to consider the problem with equanimity. For instance, patients who had had traffic accidents reported that they had first felt nervous when driving but that they drove just the same, only more carefully. People who had been struck by traffic reported that they looked around more carefully before crossing a street but that they crossed just the same. Patients who had been injured during football games decided to wear a helmet or not to play any more since they had to support their families and were anxious to avoid further work disability. Another patient who had been injured while roller skating decided to frequent a rink other than the one at which she had been injured, where better instruction was given and stricter discipline was maintained. A few patients were concerned about the physical outcome for a short while after injury. Some remembered things they had read about amnesia and thought they might forget much of their past; others worried about careless remarks which they had heard concerning the seriousness of their injury, but they were comforted after the first reassuring discussion with the physician. No one in this group had any prolonged work disability. The majority returned to work immediately after discharge from the hospital. None had any post-traumatic anxiety dreams. Thus, their reaction to the injury promoted attention, sharpened judgment and resulted in suitable measures toward self preservation. The pretraumatic, as well as the post-traumatic, adjustment to work and social obligations was undisturbed in this group. This fact and the absence of post-traumatic nightmares make it possible to forecast a favorable development of a condition which otherwise shows points

of similarity to the early stages of post-traumatic neurosis.

We estimated that of all patients with head injuries about one-third showed no psychologic reaction whatever to the injury; one-third showed apprehension resulting in a healthy adjustment and in increased measures for self preservation, while the other third reacted with the development of neurosis.

WORKING EFFICIENCY FOLLOWING INJURY IN RELATION TO PRETRAUMATIC AND POST-TRAUMATIC PSYCHIATRIC CONDITIONS

Of the 42 patients who returned to work within seven days, only 1 patient, a Negro woman, had any post-traumatic mental sequelae. Her pretraumatic alcoholism and hypochondriasis were somewhat worse after injury. Of the 71 patients returning to work within one month, the proportion with post-traumatic mental symptoms was also low, namely, 21 per cent. On the other hand, of the 60 patients whose working disability was longer than one month, the proportion with post-traumatic mental symptoms was high, namely, 65 per cent. All the 18 patients returning to work after four months had psychiatric complications. Two of the 18 patients, however, presented personality changes only, without psychogenic complications. Of the remaining 16 patients with post-traumatic neurosis, 15 had anxiety states and 1 an obsessive-compulsive condition. However, this patient who complained that after injury he had phobias and compulsions forcing him, for instance, to try over and over whether he had locked the door of his garage, was seen only once and refused to submit to further follow-up study.

These observations reveal that post-traumatic mental complications are the chief cause of long-lasting employment disability after civilian head injuries. These complications are predominantly composed of anxiety reactions.

SUMMARY AND CONCLUSIONS

Of a group of 200 patients, post-traumatic mental symptoms developed after head injury in 31.5 per cent. A number of extrinsic and intrinsic factors were examined in relation to the development of these symptoms. Pretraumatic factors having a high incidence of post-traumatic mental symptoms were advancing age, the married status in men, certain national stocks, certain occupations, the type of injury and, among the psychiatric disturbances, pretraumatic symptoms based on anxiety. Post-traumatic factors having a high incidence of post-traumatic mental symptoms were the initial occurrence of coma and post-traumatic amnesia, certain accompanying injuries, a prolonged stay in the hospital and the presence of headaches and dizziness. In particular, prolonged duration of headaches and dizziness was associated with a high incidence of mental symptoms. Other physical sequelae of the injury lasting more than six months had an equally high incidence of mental symptoms (73 per cent). Post-traumatic nightmares were regularly associated with additional symptoms of anxiety. In addition, certain environmental complications, occupational difficulties in particular, and problems of litigation and compensation were correlated with a high incidence of post-traumatic mental symptoms.

Of the patients with post-traumatic mental symptoms, the largest group, 48 patients, had post-traumatic anxiety states. Twenty-three of these patients had previously normal personalities, whereas the remainder had preexisting psychiatric liabilities. In all but 1 of these 48 patients the issue was complicated by environmental difficulties, such as occupation, litigation, etc.

The post-traumatic neuroses of all but 3 of the 26 previously normal patients conformed to the picture of anxiety neurosis. The psychiatric syndrome in patients with pretraumatic psychiatric complications varied through modification of the preexisting condition, although 19 of the 26 patients presented predominantly anxiety symptoms.

Whereas anxiety symptoms were the predominant mental features in the post-traumatic neuroses, particularly neuroses in previously normal patients, symptoms of personality change only, such as euphoria, moodiness and apathy, in addition to changes in the intellectual status, were presented by 7 patients with severe head injuries.

Mental symptoms, particularly symptoms of anxiety, are, with headaches and dizziness, the commonest symptoms in convalescence. They are also the most common symptoms relating to disability and are undoubtedly the major cause of disability, in particular of prolonged disability. A number of factors enter into the production of such anxiety symptoms, the most direct being reproduction of fears related to the injury and accentuation and elaboration of preexisting conflicts in relation to occupational and financial questions. The latter factor accounts for the delay in onset of mental symptoms observed in several patients until they had recovered physically and were again faced with their obligations.

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DELIRIUM

III. ELECTROENCEPHALOGRAPHIC CHANGES ASSOCIATED WITH ACUTE ALCOHOLIC INTOXICATION

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CINCINNATI

Previous studies of the electroencephalograms of patients with delirium have demonstrated a close correlation between changes in the electrical activity of the brain and the level of consciousness, but no correlation with the more personal aspects of behavior, such as the character or expression of anxiety, the nature of sense deceptions or the content of thought.[1] The earliest changes in the electroencephalogram consisted of a progressive decrease in the frequency to the 6 to 8 per second range. In cases of more severe delirium there were increasing irregularity, disruption of synchrony with the appearance of low voltage fast activity and, finally, development of much high voltage irregular, slow activity with a frequency of 2 to 6 cycles per second. The severity of the electroencephalographic changes was related to the intensity, duration and reversibility of the noxious factors involved and to the premorbid status of the central nervous system, but was more or less independent of the nature of the noxious agents. The electroencephalographic changes were found to be reversible to the extent to which the clinical delirium was reversible. This was true whether there was spontaneous recovery or whether certain physiologic or chemical derangements were specifically corrected, as by changes in posture, by administration of oxygen, dextrose, insulin or adrenal cortex extract or by blood transfusion.

The administration of alcohol is an easy means of producing an acute delirium which is rapidly reversible. This affords an opportunity for further study of the relation between the electroencephalogram and the level of awareness in an experimentally induced and readily reversible delirium.

Gibbs, Gibbs and Lennox[2] studied a patient in alcoholic coma and found high voltage slow waves. With recovery the record returned to normal. Davis and associates[3] studied the effects of alcohol on the electroencephalogram and on the level of consciousness in 6 normal men. They gave 2 cc. of 100 per cent alcohol (mixed with fruit juices and sugar) per kilogram of body weight over a period of one hour. Analysis of the electroencephalograms of 2 subjects by means of the Grass analyzer showed a reduction in energy on the fast side of the frequency spectrum, particularly in the range of 10 to 13 cycles per second with relatively low concentrations of alcohol. With higher concentrations episodes of slow waves (4 to 8 cycles per second) intruded into the subject's characteristic electroencephalographic pattern and appeared in the spectrum analysis as an increase of energy in the corresponding frequency band. The subject's performance on the psychometric tests was definitely impaired while the concentration of alcohol in the blood was at its height (125 to 140 mg. per hundred cubic centimeters) and for an hour thereafter, but returned approximately to normal in four or five hours. The alcohol level of the blood was still elevated (90 to 120 mg. per hundred cubic centimeters) and the modifications of the electroencephalogram were still prominent at the end of the experiment, but the subjects were fairly sober. Mirsky and associates[4] studied the electroencephalograms of 4 normal

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Major George L. Maltby, Medical Corps, Army of the United States, and Major I. Arthur Mirsky, Medical Corps, Army Air Forces, gave help in the initial formulation of this study.

1. Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, Arch. Neurol. & Psychiat. **51**:356 (April) 1944. Engel, G. L., and Romano, J.: Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, ibid. **51**:378 (April) 1944.

2. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Effects on the Electroencephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:154 (July) 1937.

3. Davis, P. A.; Gibbs, F. A.; Davis, H.; Jetter, W. W., and Trowbridge, L. S.: The Effects of Alcohol upon the Electroencephalogram (Brain Waves), Quart. J. Stud. on Alcohol **1**:626, 1941.

4. Mirsky, I. A.; Piker, P.; Rosenbaum, M., and Lederer, H.: Adaptation of the Central Nervous System to Various Concentrations of Alcohol in the Blood, Quart. J. Stud. on Alcohol **2**:35, 1941.

rabbits in which alcohol was injected intravenously. When the animals became intoxicated and comatose, diminution in amplitude and frequency of all cortical waves occurred. Occasionally large slow waves appeared. With clinical recovery the electroencephalogram returned to normal, in spite of the fact that the alcohol concentration of the blood remained unchanged.

METHODS AND MATERIALS

Seven normal subjects and 4 patients with chronic alcoholism who had occasional convulsions associated with drinking bouts were utilized for this study. One of the latter subjects was studied twice. Three of the normal subjects were given 1 Gm. of alcohol per kilogram of body weight (50 per cent solution sweetened with saccharin) followed in about eighty minutes by 0.5 Gm. of alcohol per kilogram of body weight. Four

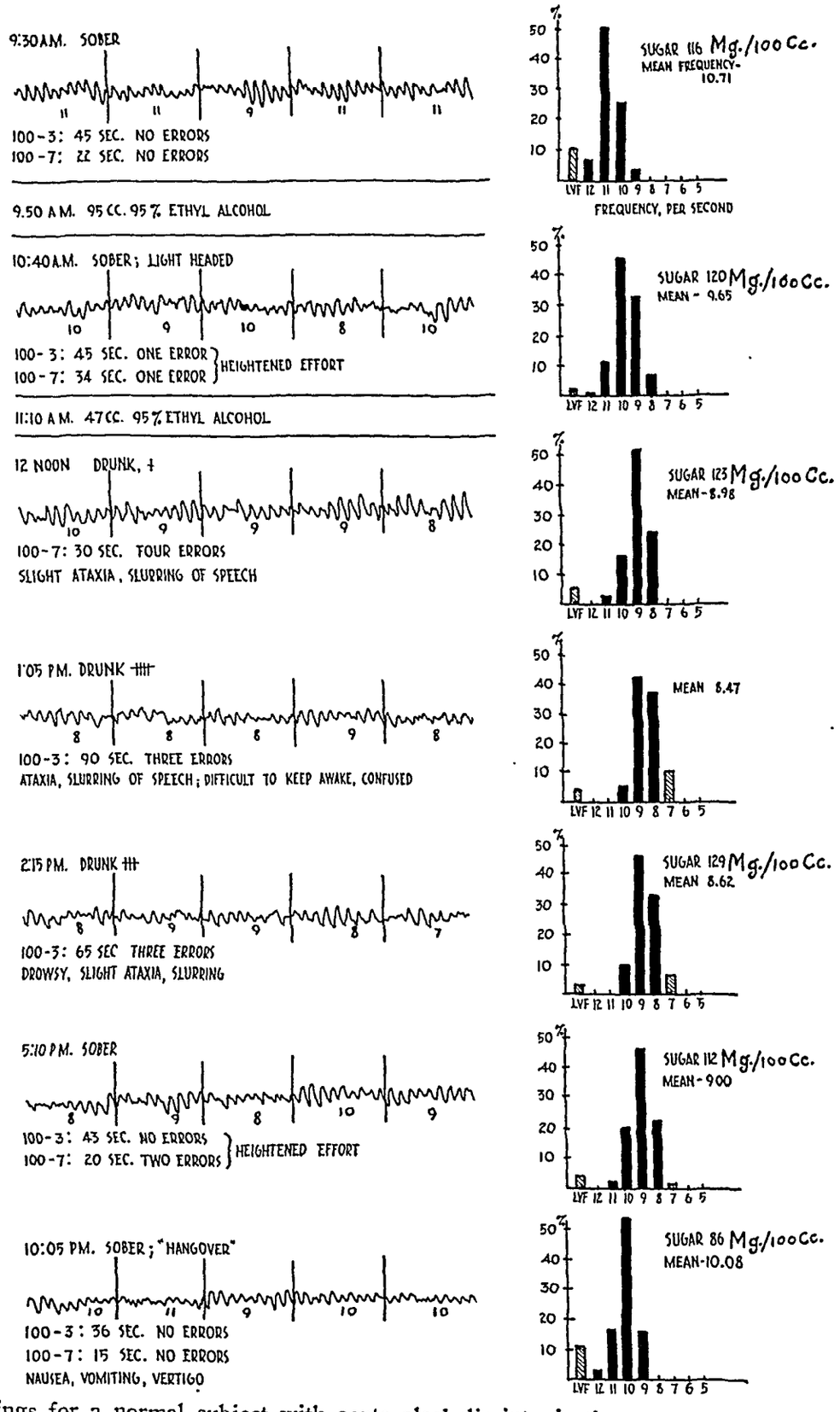

Fig. 1.—Tracings for a normal subject with acute alcoholic intoxication.

The control electroencephalogram shows high alpha activity, with a mean frequency of 10.71 waves per second. At the time of maximum intoxication (1:05 p. m.) the mean frequency had slowed to 8.47 waves per second, with 11 per cent of 7 per second activity. At 5:10 p. m. the subject was sober but still made errors when tested. The final record (10:05 p. m.), taken during a severe "hang-over," showed a mean frequency of 10.8 waves per second. The blood sugar level was 30 mg. lower than the morning control level.

normal subjects were given only the first dose and observed for only one hour. The subjects with chronic alcoholism received, in addition, a third dose of 0.5 Gm. of alcohol per kilogram of body weight between one hundred and one hundred and twenty minutes after the first dose. The alcohol was administered orally, after an overnight fast, and each dose was consumed within two to fifteen minutes. With the exceptions already noted, observations were carried out over the course of seven to twenty-five hours.

All signs and symptoms were noted, and the diagnosis was made in accordance with the criteria set down by Jetter[5] as essential for the determination of clinical intoxication. The subject was considered clinically intoxicated (+++ to ++++) when there were

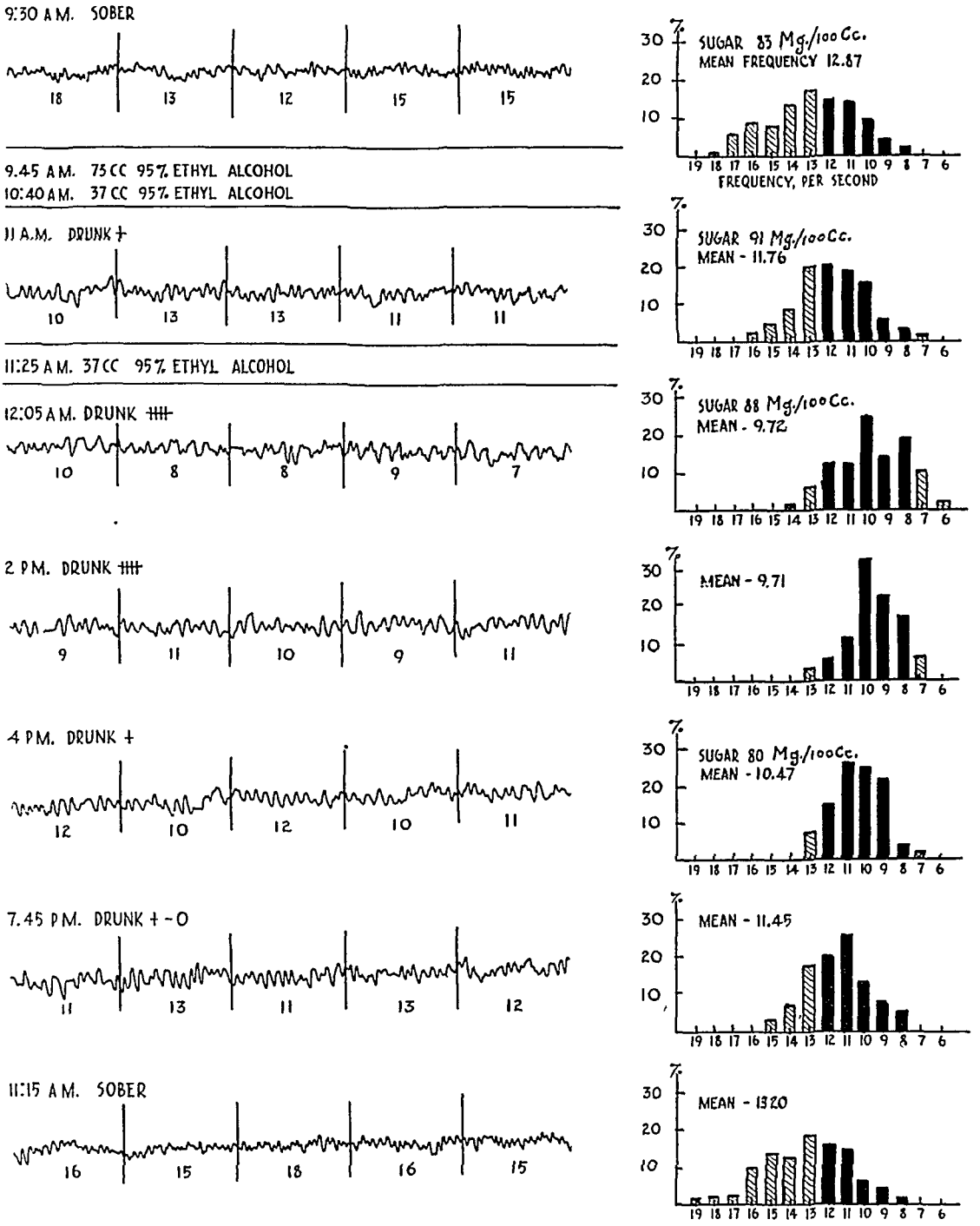

Fig. 2.—Tracings for a subject with chronic alcoholism and associated convulsions, taken during acute intoxication.

The control electroencephalogram reveals a dominant fast record (10 to 14 waves per second) with faster (15 to 18 waves per second) and slower (8 to 9 per second) activity. There were infrequent individual waves with a frequency of 6 to 7 per second which do not appear in the spectrum as such because they were added with faster waves to make the totals for each one second interval. With maximum intoxication the mean frequency shifted from 12.87 to 9.71 waves per second; twenty-five and a half hours after the first dose of alcohol, the record had returned to the control state.

5. Jetter, W. W.: Studies in Alcohol: Diagnosis of Acute Alcoholic Intoxication by Correlation of Clinical and Chemical Findings, Am. J. M. Sc. **196**:475, 1935.

abnormality of gait, ataxia, abnormality of speech, various emotional changes and gross fluctuations in the level of awareness. When the subject reported the first subjective effects of alcohol, it was recorded as 1 to 2 plus (+ to ++), the grade depending on the intensity of the symptoms, although at this stage the subject was not considered grossly intoxicated. In addition, more detailed psychologic tests to determine the level of awareness were carried out on the normal subjects. These included tests of orientation, handwriting, serial subtraction, digit span and interpretation of proverbs.

The electroencephalograph was a standard three channel, ink-writing oscillograph, constructed by Mr. Albert Grass. For the subjects with chronic alcoholism six electrodes were placed over the frontal, parietal and occipital regions on the two sides, and routine monopolar and bipolar tracings were taken to rule out the presence of focal abnormalities. For the normal subjects only bipolar fronto-occipital tracings were taken. Electroencephalograms were recorded before alcohol was given and at various intervals up to twenty-five hours after administration of the first dose of alcohol. Gross changes in the electroencephalogram were sought for by inspection. In addition, the spectrums of frequency distribution in fronto-occipital tracings were obtained by a quantitative method.[6] This method consisted in counting the number of waves per second interval for a record of two hundred seconds.

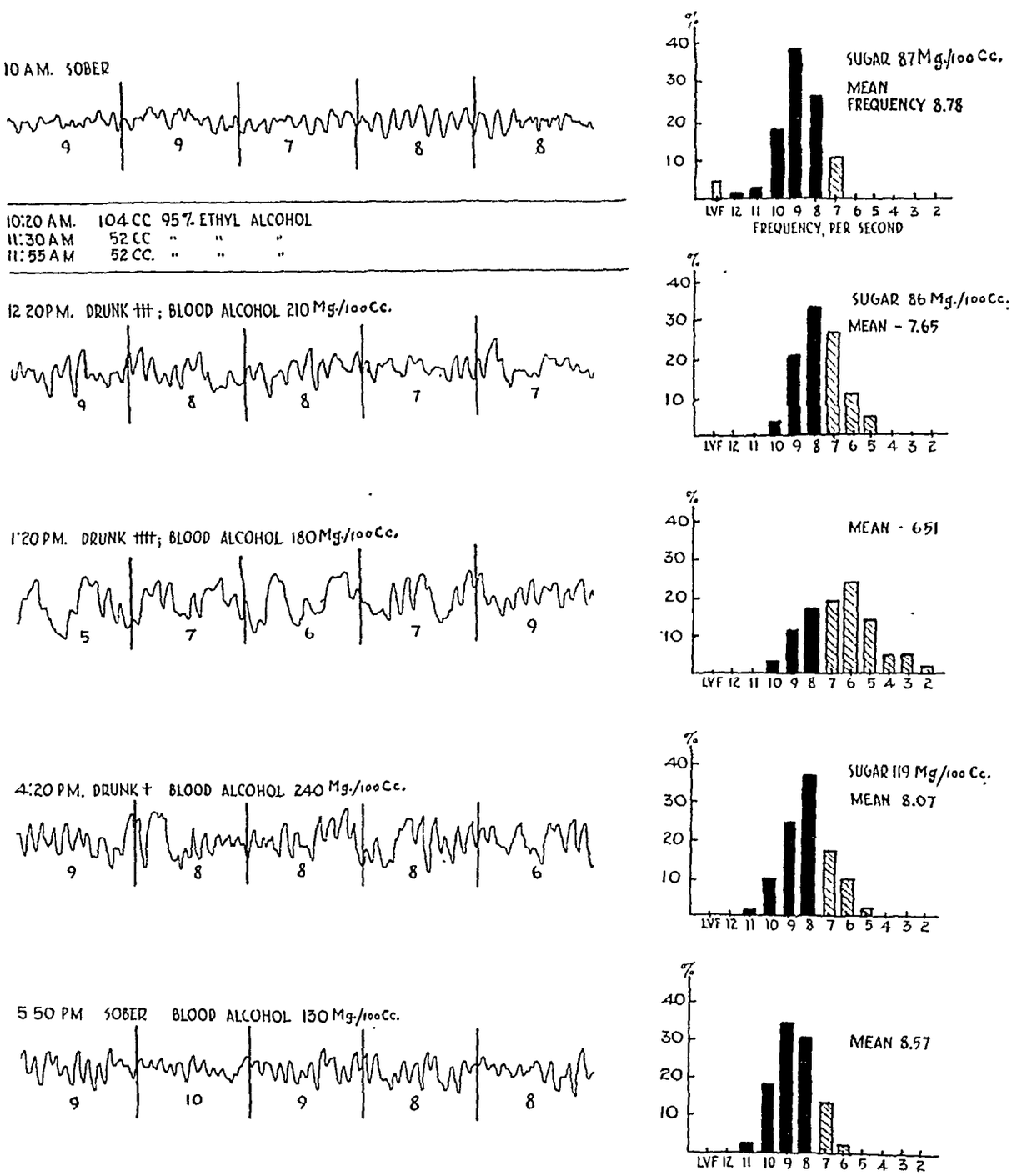

Fig. 3.—Tracings for a subject with chronic alcoholism and associated convulsions, taken during acute intoxication.

The control electroencephalogram reveals a mean frequency of 8.78 waves per second, with some slower frequencies appearing paroxysmally. With maximum intoxication slow frequencies became prominent, and the mean frequency was reduced to 6.51 waves per second.

6. Engel, G. L.; Romano, J.; Ferris, E. B., Jr.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectrums in the Electroencephalogram: Observations on Effects of Physiologic Variations in Dextrose, Oxygen, Posture, and Acid-Base Balance on the Normal Electroencephalogram, Arch. Neurol. & Psychiat. **51**:134 (Feb.) 1944.

The distribution of waves per second was then expressed as percentages of the whole, i. e., the percentages of second intervals containing 10 waves, 9 waves, 8 waves, etc. When waves faster than 12 per second were of very low voltage (less than 5 microvolts), they were all grouped together as "low voltage fast" activity. The fast waves of higher voltage were counted. Only the dominant waves that returned completely, or almost completely, to the base line were counted, the superimposed frequencies of low voltage being ignored. This method of counting is illustrated in the accompanying figures. The distribution of frequencies per second is expressed graphically as a nomogram, in which frequencies from 8 to 12 cycles per second inclusive (the so-called alpha range) are charted in black and all other frequencies in cross hatching. In addition, a value for mean frequency was obtained by averaging the distribution of waves per second interval, as expressed in the nomogram. This yields an over-all expression of frequency for each record which allows for rapid and accurate comparison of shifts in frequency under the various experimental conditions. This method has proved highly reliable in detecting even small shifts

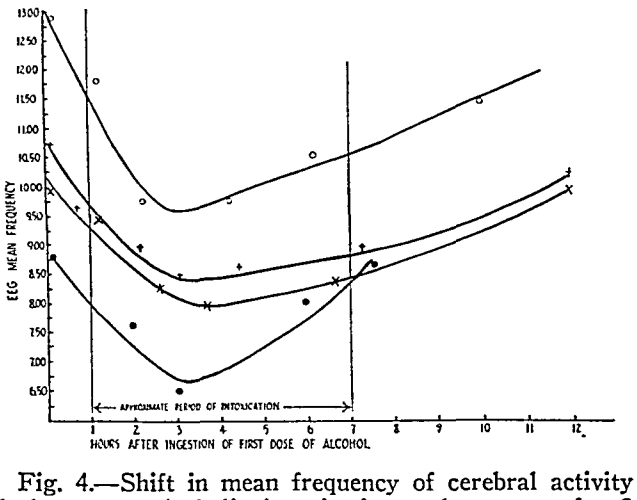

Fig. 4.—Shift in mean frequency of cerebral activity during acute alcoholic intoxication and recovery for 2 normal subjects and for 2 subjects with chronic alcoholism. All the subjects showed evidences of intoxication between the first and seventh hour.

In this graph, the curve with solid and with hollow circles indicate values for subjects with chronic alcoholism (Huc and P respectively in table); the curves with crosses and with daggers, values for normal subjects (R and S respectively in table).

in frequency distribution during manipulation of various physiologic determinants of the electroencephalogram [6] and during pathologic conditions [1] and is discussed in more detail in the references cited.

RESULTS

The development of acute intoxication followed the familiar course. The first subjective symptoms were noted by the normal subjects within forty minutes, while the subjects with chronic alcoholism generally did not acknowledge any symptoms until well into the second hour, usually after receiving the second dose of alcohol. In addition to the classic symptoms of intoxication already described, all subjects showed pronounced somnolence, from which, however, they could always be aroused. The electroencephalogram taken during this sleep did not differ from the pattern obtained during normal sleep. For the purposes of this study we kept the subjects as alert as possible during the electroencephalographic recordings by interrupting the run at frequent intervals, by talking, ringing a bell and having the subject open the eyes; no records made during sleep were included in this study. This pronounced somnolence results in an exaggerated impression of the degree of disturbance in consciousness at the period of maximum intoxication. Actually, as compared with the disturbance noted in an earlier study of delirious patients, the maximum loss of awareness as determined by the more detailed psychologic tests never exceeded what was classified as "mild" in that study.[1]

In all instances the development of intoxication was accompanied by progressive slowing of all countable frequencies in the electroencephalogram (table). The accompanying figures illustrate these changes in a normal subject whose control record showed a dominant alpha pattern (fig. 1), a subject with chronic alcoholism whose control record showed dominant high voltage fast waves with moderate amounts of 8 to 12 per second activity (fig. 2) and a subject with chronic alcoholism whose control record showed a dominant 9 to 10 per second rhythm with a moderate amount of 7 to 8 per second activity (fig. 3). The control records of the other 2 subjects with chronic alcoholism also showed abnormal patterns characterized by the admixture of fast and slow activity of moderately high voltage. Six normal subjects had normal, dominant alpha patterns, while the seventh had a mixed distribution of fast and alpha activity (8 to 15 per second). It will be noted from these figures that the changes in the level of consciousness correlated with slowing of the frequency but not with the appearance of any particular frequency. Thus, the electroencephalogram of the normal subject whose control record showed a mean frequency of 10.71 cycles (range, 9 to 12 cycles per second) revealed a shift to a mean frequency of 8.47 cycles (range, 7 to 10 cycles per second), with only 11 per cent of 7 per second waves at the height of intoxication. The record during maximum intoxication still falls within the range of accepted normality but represents a profound shift in frequency for this subject. This shift in frequency is far beyond any range previously established during alterations within physiologic zones induced by administration of dextrose and oxygen or by changes in posture for 10 normal subjects.[6] Identical results were obtained for the other normal subjects (table). Similarly, the

Subject	Experiment	Time, Min.	Blood Sugar, Mg./100 Cc.	Electroencephalographic Frequency Spectrums, Percentage of Waves per Second																	Mean Frequency per Sec.	Degree of Intoxication †
				LVF*	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2		
R. (Normal male)	Control	0	116	11	..	..	..	..	..	..	..	8	51	26	4	..	..	..	..	..	..	..	10.71	Sober
	95 cc. 95% ethyl alcohol	45	120	2	..	..	..	..	..	..	..	1	11	46	33	7	..	..	..	..	..	..	9.65	±
	47 cc. 95% ethyl alcohol	130	123	6	..	..	..	..	..	..	..	..	3	16	51	24	..	..	..	..	..	..	8.98	+
		185	...	4	..	..	..	..	..	..	..	..	..	6	42	37	11	..	..	..	..	..	8.47	++++
		265	129	3	..	..	..	..	..	..	..	..	..	10	47	33	7	..	..	..	..	..	8.62	+++
		440	112	4	..	..	..	..	..	..	..	..	3	21	47	23	2	..	..	..	..	..	9.00	Sober
		720	86	10	..	..	..	..	..	..	..	3	17	54	16	..	..	..	..	..	..	..	10.08	Sober, hang-over
S. (Normal male)	Control	0	91	8	..	..	..	..	..	..	..	..	21	46	22	3	..	..	..	..	..	..	9.92	Sober
	100 cc. 95% ethyl alcohol	70	103	1	..	..	..	..	..	..	..	..	6	45	38	10	..	..	..	..	..	..	9.47	±
	50 cc. 95% ethyl alcohol	160	123	..	..	..	..	..	..	..	..	..	..	4	35	44	17	..	..	..	..	..	8.26	++++
		225	109	2	..	..	..	..	..	..	..	..	..	3	23	46	22	4	..	..	..	..	7.99	++++
		410	111	1	..	..	..	..	..	..	..	..	..	4	35	51	9	..	..	..	..	..	8.34	++
		720	99	5	..	..	..	..	..	..	..	..	19	49	24	3	..	..	..	..	..	..	9.88	Sober
W. (Normal male)	Control	0	100	3	..	..	..	..	1	2	6	12	22	30	21	3	..	..	..	..	..	..	10.52	Sober
	95 cc. 95% ethyl alcohol	30	125	..	..	..	..	..	..	..	2	4	14	29	36	15	1	..	..	..	..	..	9.60	+
	47 cc. 95% ethyl alcohol	90	105	..	..	..	..	..	..	..	..	2	10	26	36	22	4	..	..	..	..	..	9.21	++
		165	105	1	..	..	..	..	..	..	..	2	8	15	45	24	6	..	..	..	..	..	9.01	++
		390	80	4	..	..	..	..	..	..	2	8	20	32	25	8	..	..	..	..	..	..	10.00	Sober
Re. (Normal male)	Control	0	105	9	..	..	..	..	..	..	..	11	51	24	5	..	..	..	..	..	..	..	10.75	Sober
	100 cc. 95% ethyl alcohol	45	90	5	..	..	..	..	..	..	..	3	14	58	18	2	..	..	..	..	..	..	9.98	+
B. (Normal male)	Control	0	115	..	..	..	..	..	..	..	..	5	55	39	1	..	..	..	..	..	..	..	10.64	Sober
	100 cc. 95% ethyl alcohol	50	110	..	..	..	..	..	..	..	..	..	2	44	47	7	..	..	..	..	..	..	9.41	+
Sp. (Normal male)	Control	0	100	..	..	..	..	..	..	..	..	..	..	7	69	24	..	..	..	..	..	..	8.83	Sober
	100 cc. 95% ethyl alcohol	55	110	..	..	..	..	..	..	..	..	..	..	2	39	48	11	..	..	..	..	..	8.32	±
H. (Normal male)	Control	0	105	5	..	..	..	..	..	..	..	..	1	26	55	13	..	..	..	..	..	..	9.16	Sober
	100 cc. 95% ethyl alcohol	50	105	5	..	..	..	..	..	..	..	..	..	4	30	48	13	..	..	..	..	..	8.26	+
P. (Chronic alcoholic addict)	Control	0	83	..	..	1	6	9	8	14	17	15	14	10	4	2	..	..	..	..	..	..	12.87	Sober
	110 cc. 95% ethyl alcohol	75	91	..	..	..	..	2	5	9	20	20	19	16	6	3	1	..	..	..	..	..	11.76	+
	51 cc. 95% ethyl alcohol	135	88	..	..	..	..	..	..	1	6	12	12	25	14	19	10	1	..	..	..	..	9.72	++++
		255	..	..	..	..	..	..	..	..	3	6	12	34	23	17	0	..	..	..	..	..	9.71	++++
		375	80	..	..	..	..	..	..	..	7	15	27	25	22	3	1	..	..	..	..	..	10.47	+
		600	..	..	..	..	..	..	3	7	18	20	26	13	8	5	..	..	..	..	..	..	11.45	±
		1,530	..	..	1	2	2	10	12	13	19	16	15	6	4	1	..	..	..	..	..	..	13.06	Sober
Hue. (Chronic alcoholic addict)	Control	0	87	5	..	..	..	..	..	..	..	1	2	18	38	26	10	..	..	..	..	..	8.78	Sober
	208 cc. 95% ethyl alcohol	120	86	..	..	..	..	..	..	..	..	..	..	4	21	33	26	11	5	..	..	..	7.65	+++
		180	..	..	..	..	..	..	..	..	..	..	..	3	11	17	19	24	14	5	5	2	6.51	++++
		360	119	..	..	..	..	..	..	..	..	..	1	10	24	37	17	10	1	..	..	..	8.07	+
		450	...	..	..	..	..	..	..	..	..	..	2	18	33	31	14	2	..	..	..	..	8.57	Sober

* LVF indicates low voltage fast activity.
† The degree of intoxication is graded on the basis of 1 to 4 (+ to ++++).

tracing for the subject with chronic alcoholism whose control records showed a mean frequency of 12.87 cycles (range, 8 to 18 cycles per second) showed a shift in mean frequency to 9.71 cycles (range, 7 to 13 cycles per second) at the height of intoxication (fig. 2). During the period of developing intoxication and during recovery this patient's record actually showed a higher percentage of frequencies within the so-called normal range (8 to 12 waves per second) than did his control record. This case, again, illustrates the importance of the degree of shift in frequencies rather than the absolute frequency obtained. Finally, the electroencephalogram of the subject whose control records showed dominantly slow activity (mean frequency, 8.78 cycles; range, 7 to 11 cycles per second) yielded much more slow activity (fig. 3) at the height of intoxication (mean frequency, 6.51 cycles; range, 2 to 10 cycles per second). Expressed in terms of change in mean frequency, gross intoxication was associated with a decrease in mean frequency of 2 to 3 cycles per second, regardless of the initial pattern.

The correlation between the changes in the electroencephalogram and the signs of "gross intoxication" (+++ and ++++) was good, although during the phase of recovery, when the patients described themselves as sober, the electroencephalogram had not yet returned to the control base line. However, more careful psychologic tests for the level of awareness in 3 of the normal subjects revealed minor defects at this time. With essentially similar electroencephalograms during induction of and recovery from intoxication, the performance of the subject, both subjectively and objectively, was consistently better during recovery. The reason for this discrepancy is not fully understood, but it is possible that it is more dependent on psychologic than on physiologic factors.

In the case of the subject who had a severe "hang-over," characterized by headache, vertigo on movement of the head, nausea and vomiting, the electroencephalogram had returned almost to the control pattern at the height of the "hang-over."

COMMENT

These data confirm essentially the previous observation that the earliest change of the electroencephalogram during delirium consists of a general decrease in frequency, with a shift of frequency distribution spectrums to the slower range.[1] As with the delirious patients, these early changes were not associated with any striking change in regularity. In the present studies, however, we had the advantage of knowing the character of the predelirium electroencephalogram. With this information, it is now possible to state that in correlation of the effects of noxious substances on the electroencephalogram and on the level of consciousness, the degree of change in frequency is of more significance than the appearance of any particular frequency. Indeed, with initial records that are predominantly fast, the tracing obtained during mild disturbances in consciousness may actually appear more normal than the control record. These results, again, emphasize the need for caution in the interpretation of single electroencephalograms for patients with disturbances in consciousness due to changes in cerebral metabolism.

The question whether alcohol increases the convulsive tendency, as represented in the electroencephalogram, cannot be answered by these preliminary observations on the 4 alcoholic patients with convulsions. The shift toward slow frequencies included not only the dominant elements, whether they were fast or slow, but the more paroxysmal rhythms.

SUMMARY

Acute alcoholic intoxication was induced in 7 normal subjects with normal electroencephalograms and in 4 subjects with chronic alcoholism who had occasional convulsions associated with drinking bouts and whose control electroencephalograms showed abnormally fast or slow activity. The distribution of frequencies was determined, and, in addition, the mean frequency was calculated. In all instances the development of intoxication was accompanied by progressive slowing of the brain waves, but the degree of slowing proved a more reliable index than the development of any particular wave frequency. Expressed in terms of mean frequency, gross intoxication was associated with a change in mean frequency of 2 to 3 cycles per second. When the preintoxication record was fast or fast normal, the record obtained during gross intoxication had a frequency distribution within the normal range (8 to 12 waves per second) and contained no frequencies below 7 waves per second. Indeed, some abnormally fast records became more "normal" during intoxication. With recovery the electroencephalogram returned to the preinduction status. A close correlation was demonstrated between the electroencephalogram and the level of consciousness, but not with the more personal aspects of behavior.

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ACTION OF BARBITURATES ON THE CEREBRAL CORTEX

ELECTROENCEPHALOGRAPHIC STUDIES

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BOSTON

The work of Quastel and associates [1] has shown that narcotics even in low concentrations inhibit specifically the oxidation in vitro by brain cells of d-glucose, lactic acid and pyruvic acid. This inhibitory action takes place, not by preventing the access of oxygen to brain cells nor by interfering with the activation of oxygen by brain catalysts, but by impairing the hydrogen-liberating mechanisms (dehydrogenase activity) which normally result in activation of lactic or pyruvic acid.

Narcotics inhibit this dehydrogenase activity, presumably by forming surface films or adsorption compounds which prevent the access of hydrogen donators to their activating enzymes.[2] Thus, the effect of the narcotic is to diminish the ability of the brain cells to oxidize lactic or pyruvic acid or d-glucose. The access of oxygen to the cell is quite unimpaired, but the diminished oxidizing ability of the cells results in a lowering of the amount of energy available for these cells to accomplish their functional activities. This depression of the normal functional activity of the cells in question results in, or is, "narcosis."

The chain of oxidative processes in brain cells may be represented in outline by the following simplification: At the beginning of the chain the principal substrate is d-glucose, which, through a long chain of intermediary changes, is finally oxidized to carbon dioxide and water, with liberation of large amounts of energy. One of the chief intermediary stages in the first part of the breakdown of d-glucose is the oxidation of lactic acid to pyruvic acid. Meyerhof [3] showed the dependence of this stage on the presence of a coenzyme which acts as a specific carrier linking lactic dehydrogenase with lactic acid in such a way that the dehydrogenase can remove hydrogen from the lactic acid, with the production of pyruvic acid. The dehydrogenase which activates lactic acid as a hydrogen donator is highly specific [4] and is present in greater quantities in brain than in muscle.[5]

It is this stage of dehydrogenase activity which is inhibited by narcotics of the barbiturate type. To repeat, these narcotics do not interfere with the catalytic activation of oxygen, or with the access of oxygen to the brain cells, but inhibit the activity of the dehydrogenase stages of pyruvic and lactic acid catabolism.

The mechanism of this dehydrogenase activity may well be, as Quastel and Wooldridge [6] suggested, a polarization of the molecule of the substrate by an electric field at the cell surface to which the molecule is attached. If the polarization is sufficient, the molecule will receive its critical energy of activation and will then be able to function as a hydrogen donator.

This chain of events in the cell respiration of brain tissue has been worked out from data gained from in vitro experiments with minced fresh brain and with brain slices, variations of the Barcroft and Warburg technics [7] being used for the most part. To extend these studies to the respiration of brain cells in vivo necessitates some other technic. Electroencephalography may well furnish pertinent data in this field.

From the Department of Neuropsychiatry, Harvard Medical School, and the Psychiatric Department and Electroencephalographic Laboratory, Massachusetts General Hospital.

1. Quastel, J. H., and Wheatley, A. H. M.: Narcosis and Oxidation of Brain, Proc. Roy. Soc., London, s.B **112**:60-79, 1932. Davis, D. R., and Quastel, J. H.: Dehydrogenations by Brain Tissue: Effects of Narcotics, Biochem. J. **26**:1672-1684, 1932. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135-183, 1939.

2. Sen, K. C.: The Effect of Narcotics on Some Dehydrogenases, Biochem. J. **25**:849-857, 1931.

3. Meyerhof, O.: Ueber die Atmung der Froschmuskulatur, Arch. f. d. ges. Physiol. **175**:20-87, 1919.

4. The dehydrogenase which activates lactic acid has been isolated, and its chemical constitution is known (Schlenk, F.: Whither Enzyme Chemistry, Texas Rep. Biol. & Med. **2**:183-205, 1944).

5. Green, D. E., and Brosteaux, D.: Lactic Dehydrogenase of Animal Tissues, Biochem. J. **30**:1489-1508, 1936.

6. Quastel, J. H., and Wooldridge, W. R.: Some Properties of Dehydrogenating Enzymes of Bacteria, Biochem. J. **22**:689-702, 1928.

7. Dixon, M.: Manometric Methods, London, Cambridge University Press, 1934.

The work of Hoagland [8] demonstrated clearly the influence of changes in brain cell respiration on the frequency rates of cortical potentials. It is probable that cortical cells build up potential gradients in the process of their respiratory metabolism, and, as Hadidian and Hoagland [8c] stated:

> These may be of the nature of diffusion potentials across cell membranes which possess definite electrical impedance and which discharge when the potentials reach a critical value. In such a system the discharge frequency depends on the speed with which the metabolic factor can load the capacities of the cell walls to their critical discharge potentials. The absolute frequency would thus depend on the rate of cellular respiration and on the electrical impedance of the cell walls.

The purpose of the present study was to determine whether the electroencephalogram of the intact human being would give any evidence with regard to impairment by barbiturates of cortical cell respiration or of the impedance characteristics of the cell membranes.

METHOD

Electroencephalograms were recorded by the standard method, which is too well known to need repetition here. Standard placement of six scalp electrodes was used, one electrode being placed on each frontal, parietal and occipital region. Dextrose (d-glucose) (50 Gm.) was given by mouth to every subject to insure adequate amounts of initial substrate.

A base line electroencephalogram was made with a Grass six channel ink-writing oscillograph (the heart rate being recorded on one channel), and the recording was continued through intravenous injection of the barbiturate and for approximataely one hour after its administration.

Three drugs were used: sodium amytal, sodium pentothal and sodium pentobarbital, the doses of sodium amytal varying from 0.25 to 0.65 Gm. and the doses of sodium pentothal from 0.125 to 0.5 Gm. The dose of sodium pentobarbital used was 0.3 Gm.

RESULTS

The initial effect of slow intravenous injection of any of the three drugs was completely consistent and dramatic. It was characterized by the appearance of high voltage fast activity, which is defined here as a frequency of 21 to 32 cycles per second,[9] and of voltages certainly above 25 microvolts, and frequently reaching 100 microvolts. Fast frequencies resulting from injection of sodium amytal were described by Cohn and Katzenelbogen [10] and by Rubin, Malamud and Hope.[11] Electrical activity of the kind just described was observed in every subject to whom

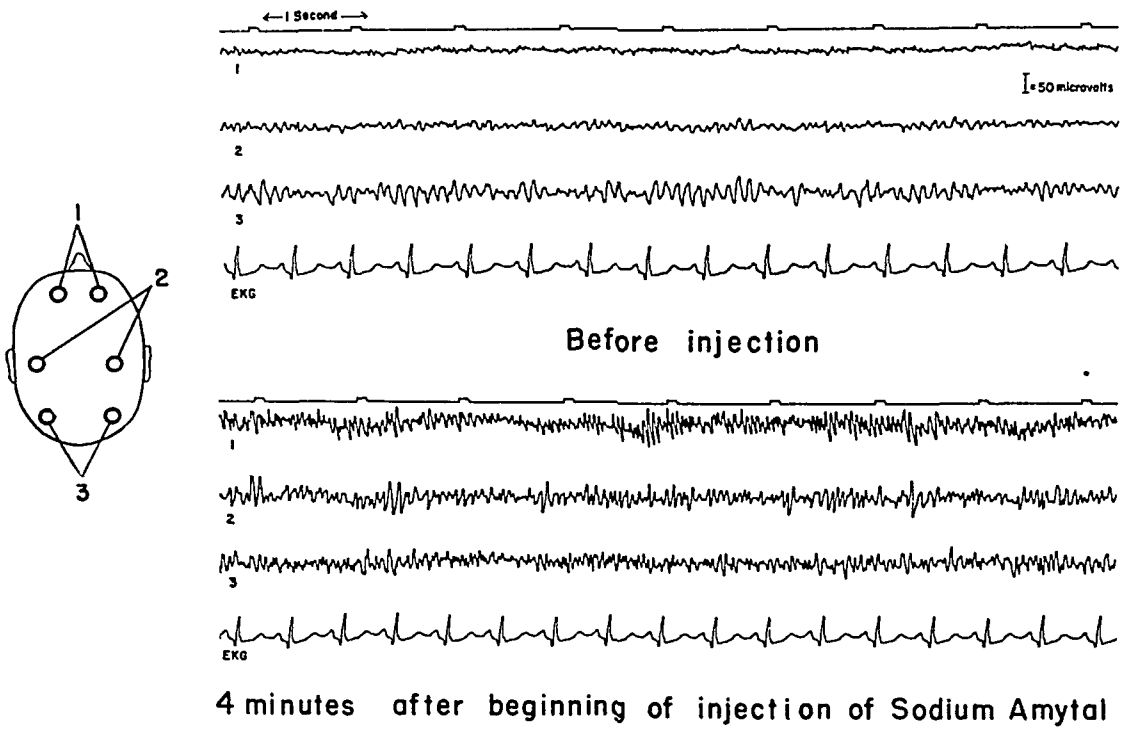

Fig. 1.—Effect of sodium amytal on the electroencephalogram.

8. (*a*) Hoagland, H.: Chemical Pacemakers and Physiological Rhythms, in Alexander, J.: Colloid Chemistry, New York, Reinhold Publishing Corporation, 1944, vol. 5; (*b*) Pacemakers of Human Brain Waves in Normals and in General Paretics, Am. J. Physiol. **116**:604-615, 1936. (*c*) Hadidian, Z., and Hoagland, H.: Chemical Pacemakers: I. Catalytic Brain Iron; II. Activation Energies of Chemical Pacemakers, J. Gen. Physiol. **23**:81-99, 1939.

9. These figures are the extremes of the range of frequencies observed. The most commonly occurring rate was 25 to 26 cycles per second.

10. Cohn, R., and Katzenelbogen, S.: Electroencephalographic Changes Induced by Intravenous Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **49**:560-563, 1942.

11. Rubin, M. A.; Malamud, W., and Hope, J. M.: Electroencephalogram and Psychopathological Manifestations in Schizophrenia as Influenced by Drugs, Psychosom. Med. **4**:355-361, 1942.

these drugs were given. Sodium amytal was given to 16 patients (twenty experiments); sodium pentothal to 22 patients (50 experiments), and sodium pentobarbital to 2 patients (two experiments). The subjects were patients from the psychiatric wards of the Massachusetts General Hospital with psychoneuroses of various kinds. There were 18 males and 16 females, with an age range of from 14 to 59 years.

In figure 1 is shown the type of electrical activity characteristic of the effect of slow administration of small doses of these drugs. In the upper record are bipolar tracings from the frontal, parietal and occipital regions respectively taken before administration of sodium amytal. In the lower record, taken four minutes after the beginning of the injection, the same leads are

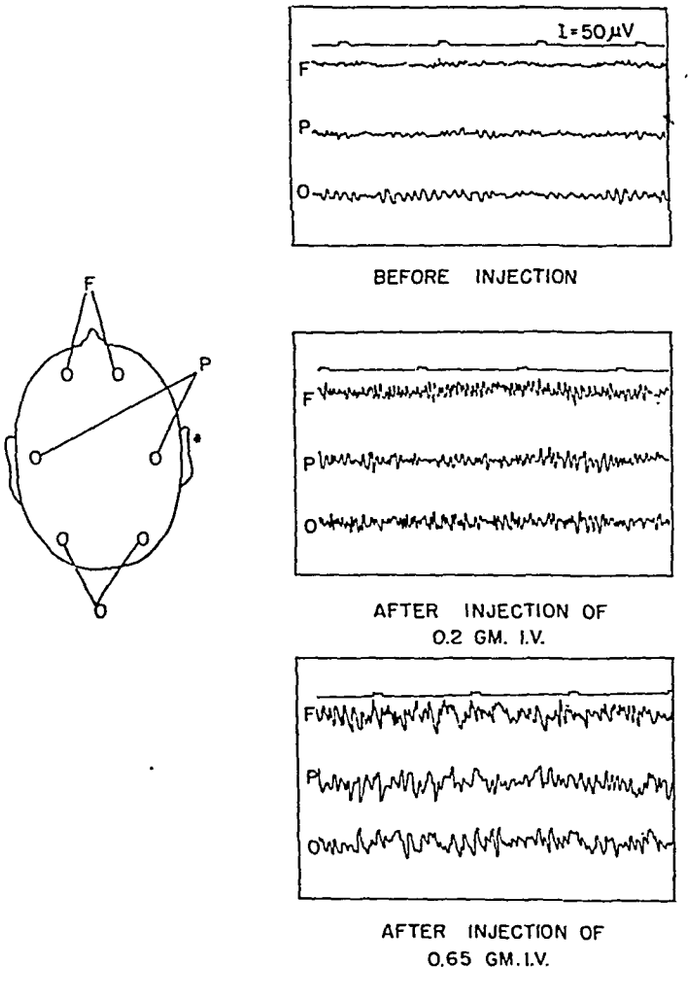

Fig. 2.—Effect of intravenous injection of sodium amytal on the electroencephalogram.

represented; here high voltage fast activity is present in every lead. The procedure employed in slow administration of the drug was to take two minutes in giving the first grain (0.065 Gm.) of the drug and from that point to administer 1 grain (0.065 Gm.) per minute. Thus, this tracing of the action of the drug four minutes after the beginning of the injection represents the effect of the injection of 3 grains (0.195 Gm.) of sodium amytal.

When a larger dose of sodium amytal was given, a second effect was seen in the electroencephalogram. This consisted of slowing of the frequencies until delta waves of 3 to 4 per second developed (see fig. 2). These were not waves characteristic of sleep and were present while the patient was still responsive.

Sodium pentothal when injected intravenously produced a similar effect. When the dose was small high voltage fast activity dominated the record, but when the dose was increased delta waves appeared.

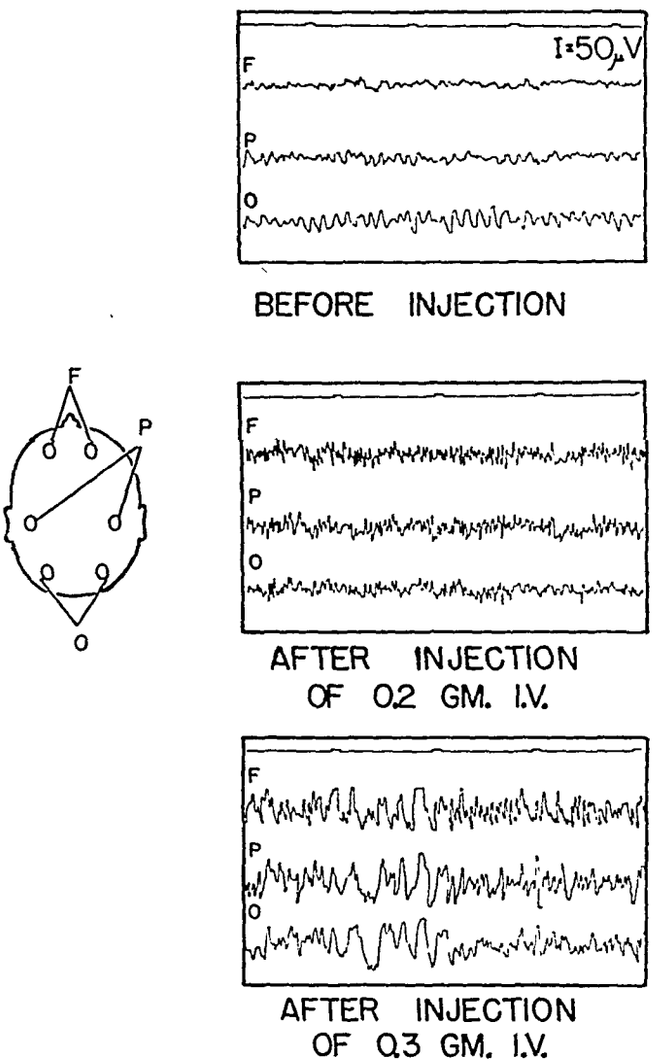

Fig. 3.—Effect of intravenous injection of sodium pentothal on the electroencephalogram.

It thus appears that barbiturates may have two distinct effects on the electroencephalogram: one, the production of high voltage fast activity by low concentrations of the drug, and the other, slowing of the frequencies when the concentration is increased. This concept of a dual effect receives support from the observation that swift administration of sodium pentothal, as in the induction of surgical anesthesia (0.2 Gm. in ten seconds), produces delta activity within one minute of the start of injection. Barbiturates are known to be rapidly destroyed in the body, so that the period of high concentration is necessarily brief.

The development of high voltage fast activity as the initial result of slow intravenous injection of these two barbiturates occurred in every subject to whom they were given, without exception. The same effect was also observed in 2 subjects who received sodium pentobarbital (0.3 Gm.) intravenously.

The development of 25 per second waves in the brain potentials of cats under anesthesia induced with pentobarbital was reported by Derbyshire and his co-workers.[12] With anesthetic doses of this drug Hoagland and associates[13] demonstrated slowing of the alpha rhythm and development of delta waves in dogs.

The most striking observation relating to the high voltage fast waves was their appearance in the electroencephalogram in various parts of the cortex at different times. In every case the effect of the drug began to manifest itself in the form of high voltage fast activity in the frontal leads before it did in any other lead (tables 1 and 2).

TABLE 1.—*Latent Period of Response* in Various Cortical Regions to Intravenous Administration of Sodium Pentothal*

Case	Dose, Gm.	Frontal Region Min.	Frontal Region Sec.	Parietal Region Min.	Parietal Region Sec.	Occipital Region Min.	Occipital Region Sec.
1	0.125	0	45	2	15	2	15
2	0.2	1	30	3	0	3	30
3	0.2	4	30	4	45	5	0
4	0.2	1	0	1	30	1	30
5	0.2	3	0	4	0	9	0
6	0.2	1	10	1	20	3	..
	0.4	0	50	1	20	3	20
7	0.25	3	0 (50 μV)	3	30	5	30
8	0.25	1	20	1	20	1	30
9	0.25	7	30	8	00	11	00
	0.5	1	10	5	00	7	00
10	0.25	..	..†	3	00	4	00
11	0.3	1	40	2	0	2	40
12	0.3	0	30	1	30	3	0
13	0.3	3	0	4	30	4	15
14	0.3	0	30	0	45	6	00
15	0.3	3	00	3	20	3	40
16	0.3	1	30	2	30	4	0
17	0.3	1	0	2	00	3	30
18	0.35	2	30	3	30	4	30
19	0.5	0	45	1	15	4	0
20	0.5	0	45	3	0	8	0
21	0.5	1	30	2	00	3	00
22	0.5	..	..†	0	45	1	00

* The arbitrary criterion of response used in this table, and in table 2, is the first appearance after the beginning of the injection of three consecutive waves each of which is above 25 microvolts.

† Not measurable because of muscle movement.

In fig. 4, the normal base line record is shown first, and the second tracing is that taken one minute after the beginning of the injection, i. e., after 0.25 Gm. of sodium pentothal had bee injected. The frontal leads already show pro nounced change, and three minutes after th beginning of the injection the change has ap peared in the parietal leads; but not until seve

TABLE 2.—*Latent Period of Response in Various Cortical Regions to Intravenous Injection of Sodium Amytal*

Case	Dose, Gm.	Frontal Region Min.	Frontal Region Sec.	Parietal Region Min.	Parietal Region Sec.	Occipital Region Min.	Occipital Region Sec.
1	0.25	5	20	6	0	No high voltage fast activity	
2	0.35	2	15	3	0	4	15
3	0.35	..	..*	3	20	4	0
4	0.35	Not recorded		3	0	Did not reach 25 μV	
5	0.45	5	0	6	30	13	30
6	0.5	2	0	5	0	Did not reach 25 μV	
7	0.5	5	0	6	0	6	20
8	0.5	5	0	5	30	6	0
9	0.5	6	20	7	0	9	30
10	0.5	6	0	7	10	7	50
11	0.5	6	30 (50 μV)	9	0	Did not reach 25 μV	
12	0.5	4	20 (15 μV)	5	0	6	20
13	0.5	Not recorded		2	10	5	30
14	0.6	4	0	5	0	7	0
15	0.65	..	..*	3	30	6	30
16	0.65	2	0	10	0	Did not reach 25 μV	
17	0.65	3	30	4	30	6	0
18	0.65	3	0	4	0	..	..
19	0.85	5	30	7	0	9	0

* Not measurable because of muscle movement.

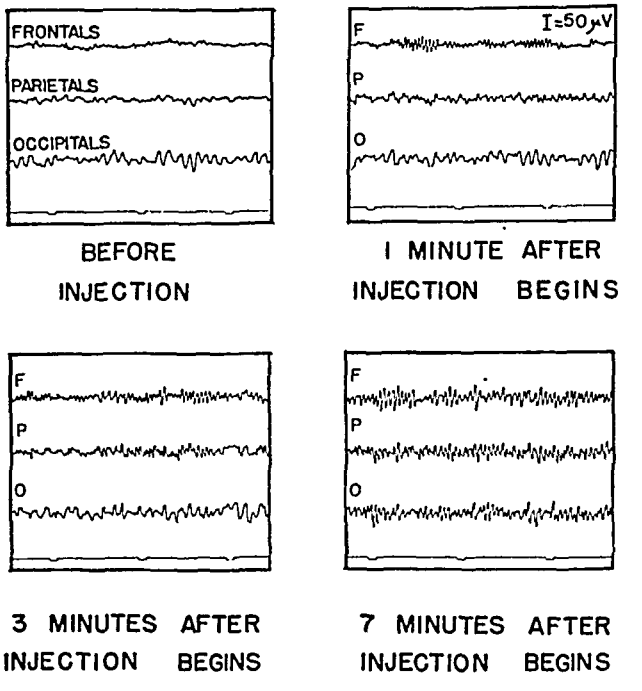

Fig. 4.—Progression of the effects of sodium pentothal in various cortical regions.

minutes after the beginning of the injection, that is, when 0.3 Gm. had been administered, did the change appear in the occipital leads. This striking progression of the effect from the frontal lobes through the parietal to the occipital region was observed in every subject to whom these barbiturates were given.

12. Derbyshire, A. J.; Rempel, B.; Forbes, A., and Lambert, E. F.: Effect of Anesthetics on Action Potentials in Cerebral Cortex of the Cat, Am. J. Physiol. **116**:577-596, 1936.

13. Hoagland, H.; Himwich, H. E.; Campbell, E.; Fazekas, J. F., and Hadidian, Z.: Effects of Hypoglycemia and Pentobarbital Sodium on Electrical Activity of Cerebral Cortex and Hypothalamus (Dogs), J. Neurophysiol. **2**:276-288, 1939.

Moreover, when the patient was allowed to recover from the effect of the drug, the regression of the effect was in the opposite direction, i. e., the occipital region recovered first, followed by the parietal areas, whereas in the frontal lobes the effect lingered for a long time.

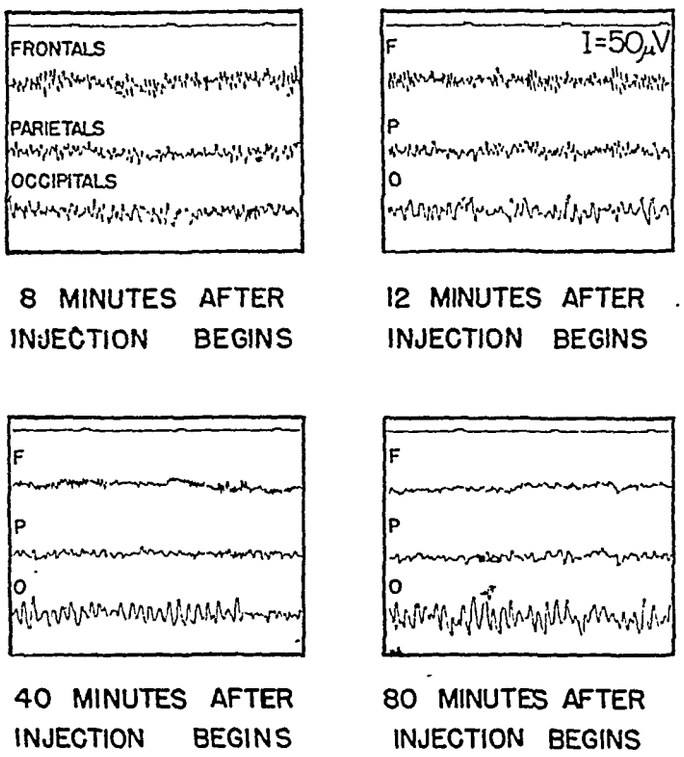

Fig. 5.—Stages in recovery from the effect of intravenous injection of 0.5 Gm. of sodium pentothal.

In the subject whose record is shown in figure 5, the occipital regions were free of high voltage fast activity within twelve minutes of the injection, but it took eighty minutes to clear the frontal lobes.

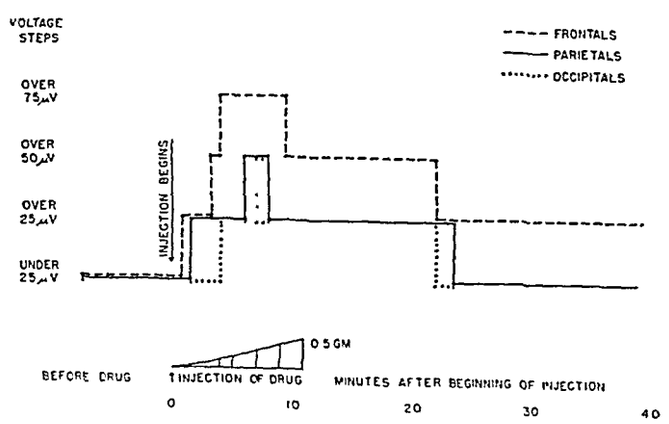

Fig. 6.—Progression and regression of high voltage fast activity in different regions of the cortex after intravenous injection of 0.5 Gm. of sodium pentothal.

In figure 6 this progression and regression of effect has been charted, and from this graph one other observation can be made. The change in the electroencephalogram from the frontal lobes not only precedes that from the other regions of the cortex but is of greater magnitude. In this graph the time relations are plotted for the development of each of three steps in the rise in voltage. The moment, timed from the beginning of the injection, at which the voltage first reaches 25 microvolts is plotted, and then the times for 50 and 75 microvolts respectively. In charting the progress of recovery, the last moment at which voltages as high as 75 microvolts were recorded is plotted; then the drop from 50 microvolts and, finally, the drop from 25 microvolts. For the subject whose record is shown in this figure, the only region of the cortex to reach voltages as high as 75 microvolts was the frontal, and forty minutes later the tracing from the frontal lead had not returned completely to the base line wave pattern.

The same effect was observed with the intravenous administration of sodium amytal, as can be seen in figure 7. Although with this drug

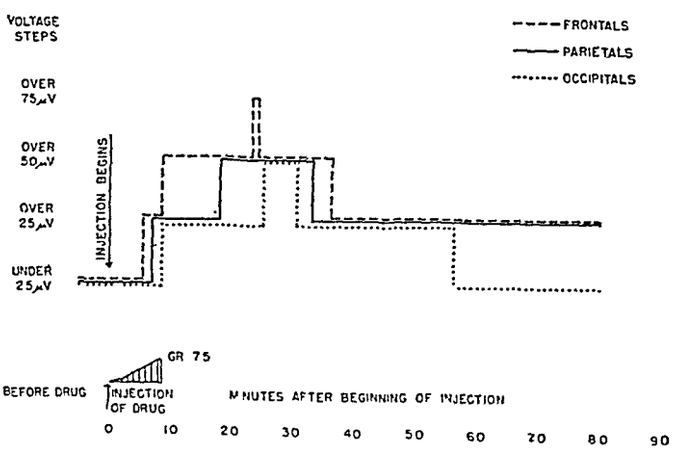

Fig. 7.—Progression and regression of high voltage fast activity in different regions of the cortex after intravenous injection of 7.5 grains (0.45 Gm.) of sodium amytal.

the change in the electroencephalogram lasted rather longer, the preponderance of the effect on the frontal lobes is again evident.

It thus appears that these barbiturates—sodium amytal and sodium pentothal—have an effect on the electroencephalogram which is most pronounced in the regions of the cortex which are of most recent ontogenetic and phylogenetic development. Salmon [14] showed that pentobarbital has less narcotic effect on young animals in which the cortical layers are not yet fully developed than on adult animals. The progression from one region of the cortex to another is too slow to be explained by differences in cerebral circulation.

Three patients were given sodium amytal by mouth in doses of 9 grains (0.585 Gm.); the electroencephalogram of 1 patient showed no effect; the second patient went to sleep and his

14. Salmon, T. N.: The Effect on the Growth Rate of Thyro-Parathyroidectomy in Newborn Rats, Endocrinology **23**:446-457, 1938.

electroencephalogram showed normal sleep waves but no other effects; the third patient's record showed all the effects observed with intravenous injection, but with a longer latent period from the time the drug was taken. High voltage fast activity appeared first in the frontal leads twenty-two minutes after the capsules were taken and reached the occipital areas in thirty-one minutes. This effect was maximal in one hour and forty-six minutes, after which delta waves appeared. There are obviously wide individual differences in reaction to the drug. At the height of the action of the drug, in the doses indicated, its effect is preponderant, and even though the patient is unconscious, the electroencephalographic record may show only high voltage fast activity. At a later stage, when the patient goes to sleep

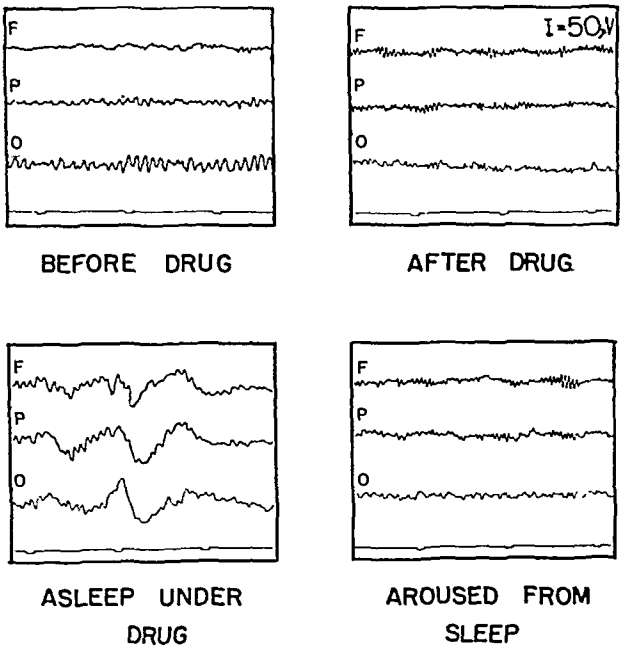

Fig. 8.—Sleep and arousal under medication with sodium pentothal.

under the influence of one of these drugs, the electroencephalogram may change from the abnormal pattern characteristic of administration of barbiturates to a normal sleep pattern (fig. 8). At this depth of sleep there is no difference between the electroencephalogram taken with the patient under the influence of the drug and that which is taken during normal sleep. But when the patient is roused from this drugged sleep, the electroencephalogram does not return to its normal pattern but shows the high voltage fast activity typical of the drug.

COMMENT

In the introduction to this paper the reasons for the design of these experiments were outlined, the essential purpose being, as stated in the final paragraph, to use the electroencephalogram in elucidation of the action of barbiturates on the respiration and on the membrane permeability of the cortical cells.

The results obtained show that the barbiturates—sodium amytal, sodium pentothal and sodium pentobarbital—influence profoundly the frequency and voltage of brain potentials in the intact human subject. Barbiturates are known to inhibit the activity of the dehydrogenase systems of cellular respiration, and changes in cellular respiration are believed to modify the frequencies of brain waves. Other agents which impede the processes of cellular respiration are known to slow the frequency of brain potentials (e. g., low blood sugar,[15] low oxygen tension,[16] cretinism [17]), whereas agents which stimulate metabolism accelerate the rhythm (thyroxin,[18] diathermy,[8b] dinitrophenol [19]). These barbiturates—depressors of activity of the central nervous system—slow the electric potentials of the brain to delta activity (3 to 4 per second) when given in such a way as to produce a high concentration in the

15. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559-570, 1937. Brazier, M. A. B.; Finesinger, J. E., and Schwab, R. S.: Characteristics of the Normal Electroencephalogram: II. The Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Quiet Breathing, J. Clin. Investigation **23**:313-317, 1944. Himwich, H. E., and others: Clinical, Electroencephalographic, and Biochemical Changes During Insulin Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **40**:401-402, 1939. Davis, P. A.: Effect on the Electroencephalogram of Alterations of Blood Sugar Level, Am. J. Physiol. **133**:259-260, 1941. Gellhorn, E., and Kessler, M.: The Effect of Hypoglycemia on the Electroencephalogram at Varying Degrees of Oxygenation of the Blood, ibid. **136**: 1-6, 1942.

16. Gibbs, F. A.; Williams, D., and Gibbs, E. L.: Modification of the Cortical Frequency Spectrum by Changes in CO_2, Blood Sugar and O_2, J. Neurophysiol. **3**:49-58, 1940. Davis, P. A.; Davis, H., and Thompson, J. W.: Progressive Changes in the Human Electroencephalogram Under Low Oxygen Tension, Am. J. Physiol. **123**:51-52, 1938.

17. Himwich, H. E.; Daly, C.; Fazekas, J. F., and Herrlich, H.: The Effect of Thyroid Medication on Brain Metabolism of Cretins, Am. J. Psychiat. **98**: 489-493, 1942.

18. Ross, D. A., and Schwab, R. S.: The Cortical Alpha Rhythm in Thyroid Disorders, Endocrinology **25**:75-79, 1939. Rubin, M. A.; Cohen, L., and Hoagland, H.: The Effect of Artificially Raised Metabolic Rate on the Electroencephalogram of Schizophrenic Patients, ibid. **21**:536-540, 1937. Himwich and others.[17]

19. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Brain Wave Frequencies and Cellular Metabolism: Effects of Dinitrophenol, J. Neurophysiol. **2**:170-172, 1939.

brain, but the initial, and more striking, effect is the breaking of high voltage fast activity into the record, not as an acceleration of the original frequency, but as a new rhythm already established at a frequency higher than 20 cycles per second. In other words, there is no gradation through the intermediate frequencies between the normal alpha rate and the ultimate fast activity.

This suggests that two effects may be taking place; if one is interference with the dehydrogenase systems, the other may be a change in permeability of the cell membrane.

The cortical cells are separated from each other and from the substrate-bearing blood supply by semipermeable membranes; it is at these surface interfaces that the enzyme mechanisms previously outlined operate—it is here that the dehydrogenase becomes "activated," i. e., changes its electronic structure in such a way that electrons become available for the oxidation of the substrate. In fact, this transfer of electrons is the fundamental mechanism, which in popular speech is called the "liberation of energy." It is actually the transfer of electrons by steps, from the system of more negative potential to the system of more positive potential until finally molecular oxygen is reached.[20]

When the metabolic oxidations in the brain are regarded from this basic electronic viewpoint, the importance of the characteristics of the surface interfaces becomes obvious.

It has long been known that narcotics decrease the permeability of cell membranes; Lillie,[21] in 1912, concluded that they caused an alteration in the surface membrane, and hence in the intracellular respiration, since reactions inside the cell are governed by the surface conditions. This conclusion has since been amply confirmed by Gellhorn and Weidling,[22] by Winterstein[23] and others.

Not only does the change in total permeability of the cell affect the internal chemical processes, but the changes in differential permeability are also influential. For example, a relatively greater increase in permeability for lactic acid with a relatively smaller increase in permeability for oxygen would result in an increase in the ratio of glycolysis to total oxidation in a cell.[24]

No change in cell permeability of this magnitude is likely without a resultant effect on the electroencephalogram, since however dependent the frequency of brain waves may be on chemical velocity within the cells, the ultimate rate of oscillation will also be governed by the impedance characteristics of the cell membrane.

It is likely that there may be two effects at work—one, the depressant effect of barbiturates on the dehydrogenase mechanisms, and the other, their effect on the dielectric of the cell membrane.

Elucidation of the relative importance of these two factors might be obtained from experiments designed to by-pass in some way one of these effects. Such a series of experiments, based on the substitution for dextrose of a substrate the dehydrogenase system of which is not vulnerable to barbiturate poisoning, is now in operation. A suitable substrate is available in the form of succinic acid; this acid, too, has its specific dehydrogenase, but its activity is not inhibited by narcotics.

It is reasonable to speculate that if the frequencies of brain potentials were dependent solely on intracellular respiration, it should be possible to maintain the rate of oscillation of these waves at the normal level in spite of the presence of barbiturates provided the cells were supplied with sufficient substrate in the form of succinate. If the resistance and capacity of the dielectric composing the cell wall were the preponderant factor in narcosis, it would be improbable that the frequencies of brain waves could be maintained at normal rates even by substrates invulnerable to barbiturates.[25] This

20. Barron, E. S. G.: Mechanisms of Carbohydrate Metabolism, in Nord, F. F., and Werkman, C. H.: Advances in Enzymology, New York, Interscience Publishers, Inc., 1943, vol. 3, pp. 149-189.

21. Lillie, R. S.: Antagonism Between Salts and Anesthetics, Am. J. Physiol. **29**:372-397, 1911-1912.

22. Gellhorn, E., and Weidling, K.: Beiträge zur allgemeinen Zellphysiologie, Arch. f. d. ges. Physiol. **210**:492-513, 1925.

23. Winterstein, H.: Die Narkose, Berlin, Julius Springer, 1926.

24. Rashevsky, N., and Landahl, H. D.: Permeability of Cells: Its Nature and Measurement from the Point of View of Mathematical Biophysics, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1940, vol. 8, pp. 9-16.

25. In discussing our results, Hoagland (in a personal communication) suggested an alternative possibility to account for the appearance of high voltage fast rhythms despite probable over-all slowing of cortical respiration. He suggested that the fast rhythms may be due to the accumulation in the cells of lactate, since the barbiturates block its oxidation. Such an accumulation would raise the internal acidity of the cells. He expressed the opinion that the relation between cell respiration and frequency of brain wave rhythms is normally mediated by production of carbon dioxide, and he pointed out that the internal p_H of the cortical cells may determine their frequency of discharge, as it may in the respiratory center. Accumulation of lactic acid resulting from blockage of oxidation of lactate might lower the intracellular p_H and raise the frequency of the discharge.

problem is the subject of an investigation at present being carried out.

SUMMARY

In this study the electroencephalogram has been used in an attempt to elucidate the mechanics of cortical cell respiration in vivo.

One of the barbiturates—sodium amytal (in twenty experiments), sodium pentothal (in fifty experiments) and sodium pentobarbital (in two experiments)—was given intravenously to 32 patients.

For every subject to whom the barbiturate was given the electroencephalogram showed the development of high voltage fast activity.

In the patients who received larger doses per kilogram of body weight a second effect developed; this consisted of slow delta waves (3 to 4 per second).

In every subject the high voltage fast activity appeared first in the frontal leads, then in the parietal leads and finally in the occipital leads, and it disappeared in the reverse order. In other words, the regions of the cortex which are the most recent in phylogenetic development are most vulnerable to the action of barbiturates, as evidenced by the electroencephalogram.

In the first few minutes of injection, at the stage of maximal action of the drug, the patient may be unconscious without the appearance of any of the brain waves typical of sleep. At a later stage the patient may sleep deeply under the influence of the drug, at which time the electroencephalogram may show typical waves for normal sleep, but on the patient's arousal it will revert to the high voltage fast activity specific for the barbiturate.

ENCEPHALITIS ASSOCIATED WITH HERPES ZOSTER

REPORT OF A CASE

SIGMUND KRUMHOLZ, M.D., AND JOSEPH A. LUHAN, M.D.
CHICAGO

This case is reported because the literature contains few records of cases of encephalitis complicating herpes zoster in which the brain was examined histologically after death.

REPORT OF CASE

History.—Mrs. L. V., a housewife aged 58, white, was seen by one of us (S. K.) in consultation on April 6, 1942, because she had become restless, noisy and irrational. She had been in relatively good health except for occasional headaches and backache, for which she was taking acetylsalicylic acid. On March 7 neuralgic pain developed in the left side of the face and neck. Two days later examination by the family physician revealed a herpetic rash over the lower part of the face, the neck and the upper part of the shoulder and chest on the left side. The patient had a slight fever (temperature 99.5 to 100.0 F.) for several days. The vesicles disappeared in about fourteen days, but the pain persisted. On April 4 she complained of restlessness and insomnia. The next day she became irrational and noisy. On that day Dr. Maurice Oppenheim, a dermatologist, was called in consultation and concurred in the diagnosis of herpes zoster, expressing the conviction that the patient now presented a cerebral ailment. Nothing in the history relative to previous diseases and habits had any apparent bearing on the present illness.

Physical Examination.—Examination on April 6 by one of us (S. K.) revealed that the patient was well preserved. She was lying in bed and presented marked clouding of consciousness, accompanied by extreme restlessness. She did not respond to psychic stimuli, such as requests to protrude the tongue; she moaned, tossed about on the bed incessantly and reached out with her arms aimlessly into space. She was obviously out of contact with her environment but was not somnolent. There was pigmentation of the skin, involving the left side of the neck, the shoulder and the uppermost part of the chest, as well as the submental region and the lower portion of the face adjacent to the ear, an area representing the second, third and fourth cervical dermatomes. The rectal temperature on the morning of examination was 104.6 F.; the pulse was regular, with a rate of 120, and the respiratory rate was 34 per minute. The cardiac outline was within normal limits, and the heart presented no adventitious sounds. Except for bronchial rales the lungs were normal. The abdomen was not tender. The spleen and liver were not palpable. The blood pressure was 125 systolic and 80 diastolic.

Neurologic Examination.—The pupils were small and equal and reacted to light. The patient could not cooperate in tests of ocular motion, but no strabismus or nystagmus was observed. The corneal reflex was present on both sides. There was no facial paralysis, nor was there any masking or rigidity of facial expression or rigidity of the trunk and extremities, such as one sees in paralysis agitans. It was impossible to determine whether the patient had any weakness of the soft palate or of the swallowing musculature. The tongue lay in the midline. The fundi could not be seen. There was no discernible paralysis of the extremities or detectable muscle spasm on passive movements. The biceps and triceps reflexes were graded 2 plus; the patellar and achilles jerks were diminished. No pathologic reflexes were noted. There was withdrawal of the extremities and face to painful stimuli. Deep pressure on the calves of the legs produced withdrawal of the lower extremities. There was no significant nuchal rigidity. Kernig and Brudzinski signs were absent.

Laboratory Data.—The white blood cells on April 6 numbered 8,200 per cubic millimeter, of which 70 per cent were neutrophils, 29 per cent lymphocytes and 1 per cent large mononuclears. The erythrocyte count was 4,500,000 per cubic millimeter, and the hemoglobin concentration was 88 per cent (Tallqvist). A catheterized specimen of urine obtained on that day revealed no albumin or sugar, but the sediment contained a small number of granular casts and pus cells. Culture of a specimen of blood taken the same day revealed no growth when examined on April 13. The Kahn reaction of the blood was negative. The nonprotein nitrogen was 38.4 mg. per hundred cubic centimeters.

Spinal puncture performed later in the day revealed a cell count of 40 per cubic millimeter, of which 80 per cent were lymphocytes and 20 per cent polymorphonuclear leukocytes. The Pandy reaction of the spinal fluid was 1 plus; the Lange curve, 1110000000, and the dextrose content, 111 mg. per hundred cubic centimeters. (On the previous day the patient had received 1,500 cc. of a 5 per cent solution of dextrose, given intravenously.) The Wassermann reaction with 1 cc. of spinal fluid was negative.

Diagnosis.—It was the impression of the examiner that the patient had nonsuppurative encephalitis, although the possibility of a toxic psychosis was to be considered. In view of the relative absence of objective neurologic signs of a cerebral lesion, the diagnosis of encephalitis was reluctantly made. However, the acute nature of the disease, with high temperature, the presence of 40 cells per cubic millimeter in the spinal fluid at the receding stage of the herpes zoster, the absence of signs of infectious disease of the visceral organs and the lack of evidence incriminating any metabolic or exogenous toxic agent made the diagnosis of encepha-

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Read at a meeting of the Chicago Neurological Society, Oct. 15, 1942. An abstract of this paper, with discussion was published in the April 1943 issue of the ARCHIVES, page 633.

litis plausible. It is well known that neither encephalitis nor toxic encephalopathy produce a uniform clinical picture; the former, especially in the early stage, may show no objective focal neurologic signs, and the latter may at the onset present focal signs of cerebral disease.

Further Clinical Course.—The patient continued to be noisy and restless and moaned almost incessantly. On April 8, 9 and 10 she had periods of loud screaming. Involuntary urination occurred on April 9 and continued until her death. The nurses' records show that from time to time she was able to swallow sips of water and small quantities of liquid food. On April 6 sulfadiazine therapy was begun, which was discontinued on April 9, when the level of the drug in the blood was reported to be 3.1 mg. per hundred cubic centimeters. The rectal temperature remained in the vicinity of 102 F., rising above 104 F. two days before she died and reaching an agonal value of 108.6 F. The respiratory rate stayed rather constantly at about 30 per minute except on the last three days of her illness, when it rose to and remained over 40 to 50 per minute, the curve reflecting perhaps the development of bronchopneumonia. The patient died on April 15.

Gross Pathologic Study.—Necropsy was performed nine hours after death by Dr. Benjamin Neiman, who made the following anatomic diagnosis on the basis of the macroscopic observations: (1) fibrinous pericardosis; (2) pronounced parenchymatous degeneration of the myocardium; (3) bronchopneumonia involving the right lung; (4) fatty changes in the liver; (5) arteriosclerotic cysts of the kidneys; (6) fibrous adhesions of both pleural cavities, and (7) nodular goiter.

The fresh brain weighed 1,150 Gm. The leptomeninges were notably injected. The convolutions appeared somewhat flattened, and the leptomeninges were less transparent than normal. The lateral ventricles were of average width, and their lining was smooth.

We regret that the spinal cord, the ganglia of the posterior spinal roots and the gasserian ganglia were not obtained.

Microscopic Examination.—Examination of numerous sections from many blocks from all lobes of the brain, the subcortical white matter, the basal ganglia and the hypothalamus, stained with cresyl violet and with hematoxylin and eosin and by Weil's method for myelin sheaths, revealed no significant perivascular infiltrations in the meninges or the brain tissue and no demyelination. There were moderate edema and hyperemia of the leptomeninges of the convexities (fig. 1). Over the prefrontal convexities there was proliferation of arachnoid cells in the edematous meninges; small numbers of scavenger cells containing blood pigment were present, and deposition of hemosiderin within the cells of the first two cortical layers had occurred. There were conspicuous shrinkage spaces about the cortical ganglion cells, and in most of the cortical sections the larger ganglion cells showed powdery dissolution of Nissl substance and a

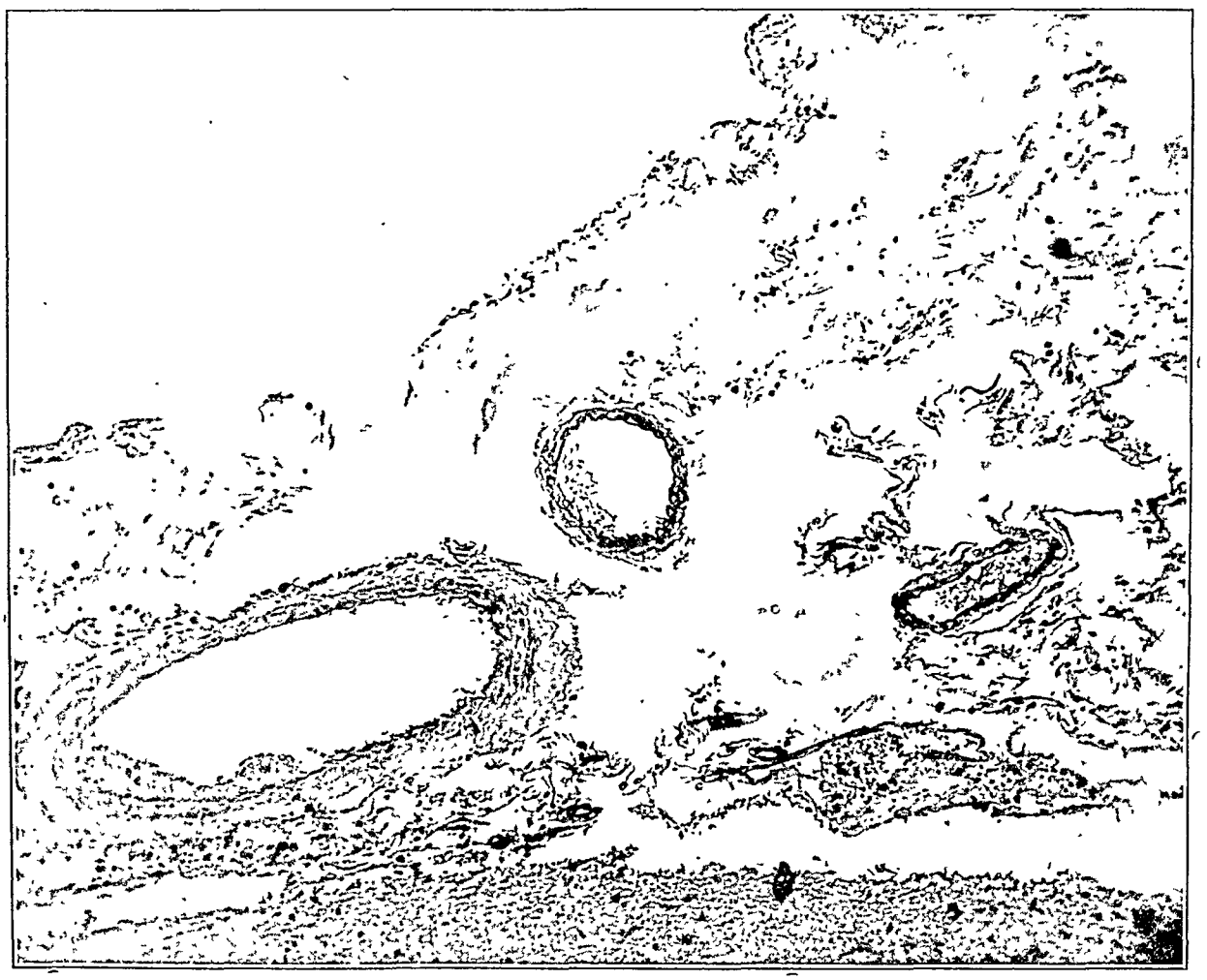


Fig. 1.—Section from right parietal region, showing edema of the surface leptomeninges. Hematoxylin and eosin stain.

picture resembling that of "acute ganglion cell disease" (fig. 2). In some cortical areas, especially the parietal, there was slight glial hyperplasia, especially of the satellite cells. Throughout the cortical sections the capillary bed was conspicuous, often with swelling of the endothelium. The white matter underlying the ependymal surfaces of the ventricles was distinctly hydropic. The basal ganglia and the hypothalamus revealed no signs of a proliferative type of encephalitis.

Similarly, the midbrain, the pons (including the entering fifth nerve trunk) and the cerebellum were free from any infiltrative changes.

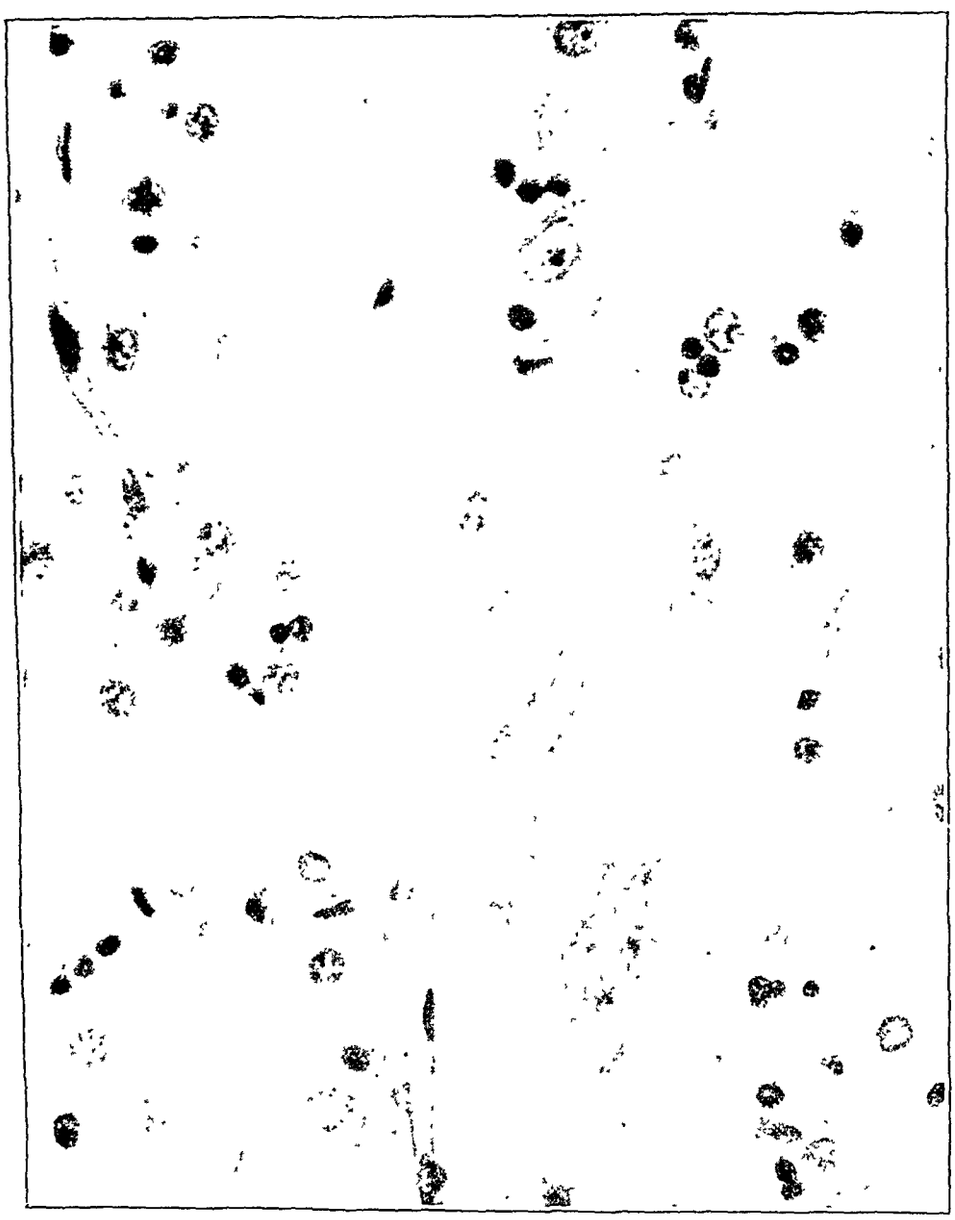


Fig. 2.—Section of right parietal cortex, revealing picture of "acute ganglion cell disease" in the larger pyramidal cells, slight glial hyperplasia and prominent capillaries. Cresyl violet stain.

The medulla oblongata, however, presented unmistakable evidence of mild encephalitis, or meningoencephalitis, most pronounced at the midolivary level. There were occasional perivascular infiltrations in the leptomeninges and loose small round cell infiltrations, the latter occurring near the ventromedian surface of the medulla. The neural parenchyma contained infrequent round cell infiltrations within the adventitial (perivascular) spaces (figs. 3 and 4), near the olives, in the lateral reticular formation and the restiform bodies; in the caudal portion of the medulla these infiltrations were limited to the region of the cuneate fasciculus of one side. Scattered minute foci were noted on the other side, where small demyelinated areas lay adjacent to the olive. These tissue foci (figs. 5 and 6) revealed conspicuous glial proliferation, with the development of predominantly microglial forms, as shown by their polyblastic and rod-shaped nuclear structure. Occasional lymphocytes adjacent to capillaries were seen in these foci. The capillary endothelium showed conspicuous swelling and proliferation, so that it was sometimes difficult to distinguish microglial rods from capillary endothelium. The ganglion cells in these foci appeared swollen, sometimes with eccentric nuclei; and a minority of these cells had undergone neuronophagia. The demyelinated foci, which were most pronounced near the olive on one side (figs. 7 and 8) appeared to merge gradually with the normal white matter and actually consisted of areas in which nerve fibers had been destroyed; the cresyl violet stain revealed a dearth of nuclei, capillary swelling and slight marginal proliferation of glia. Lower in the medulla a minute focus of demyelination was seen near the cuneate fasciculus on one side, with compound granular corpuscles between the degenerating myelin fibers.

COMMENT

The pathologic evidence in this case undeniably establishes the presence of relatively mild

nonpurulent encephalitis of the medulla oblongata but fails to demonstrate an infiltrative type of inflammatory reaction in the brain above the medulla. The histologic changes in the cerebral cortex are like those observed in many instances of toxic psychosis or toxic encephalopathy, essentially edematous changes which do not seem adequately to reflect the violence of the clinical picture. The question arises whether the anatomically demonstrable mild encephalitis and the clinical picture of a toxic psychosis, with its minimal histologic substratum, were indeed produced by one causative agent, namely, the virus of herpes zoster. It might well be argued that the encephalitis of the medulla oblongata was the consequence of an upward extension of the zosteric inflammatory process beyond its traditional confines of the cervical dorsal root ganglia, and perhaps the ipsilateral regional posterior gray matter of the cord, and that, independent of the zona, the patient had a toxic psychosis, perhaps the result of pneumonia. However, the terminal pneumonia was not clinically demonstrable until a few days before the patent's death, and no other source of toxemia was revealed clinically or at necropsy. The fibrinous pericardosis was considered a terminal development.

It is most reasonable to assume that the inflammatory reaction within the medulla oblongata was indicative of the presence therein of the virus of herpes zoster (after its intraneural dissemination rostrad from the ganglionitis of the upper cervical ganglia and the posterior poliomyelitis). It is plausible, furthermore, that in this apparently allergic patient the toxin of the virus of herpes zoster was the etiologic factor in the toxic psychosis or toxic encephalopathy. In this general connection, Finley,[1] in a study of the problem of pathogenesis of encephalitis occurring with vaccination, smallpox and measles, showed evidence in support of the belief that these encephalitides are allergic responses of the central nervous system to the virus of the exanthems. In our case the very mildness and the general histopathologic appearance of the changes in the medulla oblongata suggest that the process here was regressing. This is in accord with the interpretation that the encephalitis of the medulla antedated the cortical encephalopathia, the latter being an allergic complication of the former.

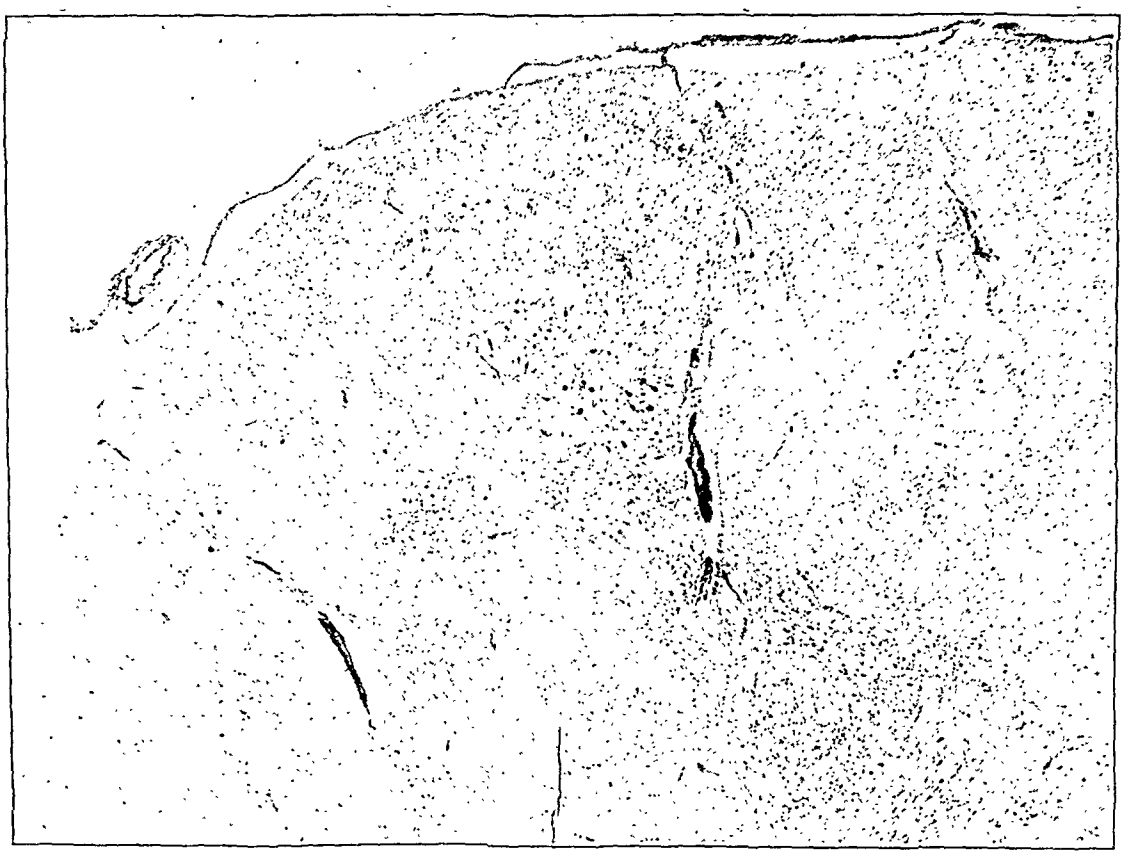


Fig. 3.—Low power view of the medulla, region of the lateral cuneate nucleus, showing perivascular infiltrations. Cresyl violet stain.

1. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

Cases of encephalitis of presumed zosteric origin with histopathologic studies of the brain are rare. The best known cases are those of Thalhimer [2] and Biggart and Fisher.[3] In both these cases there was relatively little infiltrative inflammatory reaction in the cerebral cortex, and cerebral symptoms developed more than a month after onset of the herpes. In our case the mental symptoms appeared in the course of the receding stage of the herpes zoster, about one month after its onset.

Fig. 4.—Perivascular infiltration in the caudal portion of the medulla near one cuneate fasciculus. Cresyl violet stain.

Thalhimer's [2] case was that of a woman aged 72 who became weak and drowsy six weeks after onset of herpes zoster over the right side of the neck and died a week later. Necropsy revealed prominent perivascular areas of infiltration in the cord, with a decreasing degree of involvement through the medulla and pons, occasional foci of infiltration in the basal ganglia and none in the cortex.

Biggart and Fisher [3] described the case of a man aged 63 who five weeks before had an attack of herpes zoster involving the right buttock and thigh; the patient was drowsy and delirious on admission to the hospital and died on the fifth day. Necropsy disclosed perivascular infiltrations in the posterior portion of many segments of the cord and the lumbar dorsal root ganglia; there was slight involvement of the brain stem, the cerebellar nuclei, the thalamus, the hypothalamus and the parietal cortex. Yet the cortex in the main presented only chromatolysis.

A less convincing case of encephalitis of presumed herpetic origin was reported by Anderson and Wulff [4]; in a woman aged 80, two or three weeks after the appearance of herpes zoster of the left arm, there developed paresis of the left arm, anesthesia over the left side of the face, difficulty in swallowing and

2. Thalhimer, W.: Herpes Zoster: Central Nervous System Lesions Similar to Those of Epidemic (Lethargic) Encephalitis: Report of a Case, Arch. Neurol. & Psychiat. **12**:73 (July) 1924.

3. Biggart, J. H., and Fisher, J. A.: Meningo-Encephalitis Complicating Herpes Zoster, Lancet **2**: 944, 1938.

4. Anderson, M. S., and Wulff, F.: Meningitis serosa und Encephalitis bei Zoster, Acta psychiat. et neurol. **8**:213, 1933.

speech disturbance, with an atypical Babinski sign on both sides. She died of bronchopneumonia three and a half months after the appearance of the herpes. Necropsy revealed no proliferative inflammatory foci in the brain, although sporadic lymphocytic infiltrations were seen about the pial vessels of the anterior median fissure and around capillaries of the nerve roots.

Bellavitis [5] reported the case of a psychotic patient aged 53 who had been alcoholic and in whom cutaneous herpes zoster had suddenly developed in the distribution of the second to the fourth cervical segments on the left side. Eight days later palsy of peripheral type appeared on the same side of the face, and a few days later hemiparesis developed on the left side. Necropsy revealed cirrhosis of the liver and congestion of the central nervous system, particularly the cervical posterior root ganglia on the left side. Microscopic study revealed hyperemia, hemorrhage, perivascular lymphocytic infiltration and neuroglial proliferation, especially in the cervical portion of the cord, and also in the medulla and the pons. The posterior horn cells in the cervical part of the cord appeared diseased.

Roger, Poursines and Paillas [6] reported a case of poliomesencephalomyelitis marked clinically by multiple palsies in the distribution of the cranial nerves, which developed after herpes zoster of the external ear. The patient died of failure of medullary function ten months after the onset of the illness. Necropsy revealed inflammation of the posterior gray matter of the first cervical segment and small lesions with telangiectatic proliferation in the white matter of the medulla and pons.

Schiff and Brain [7] reported a fatal case of acute meningoencephalitis associated with herpes zoster in which necropsy was not done. In a man aged 67 there developed herpes zoster, the cutaneous lesion affecting

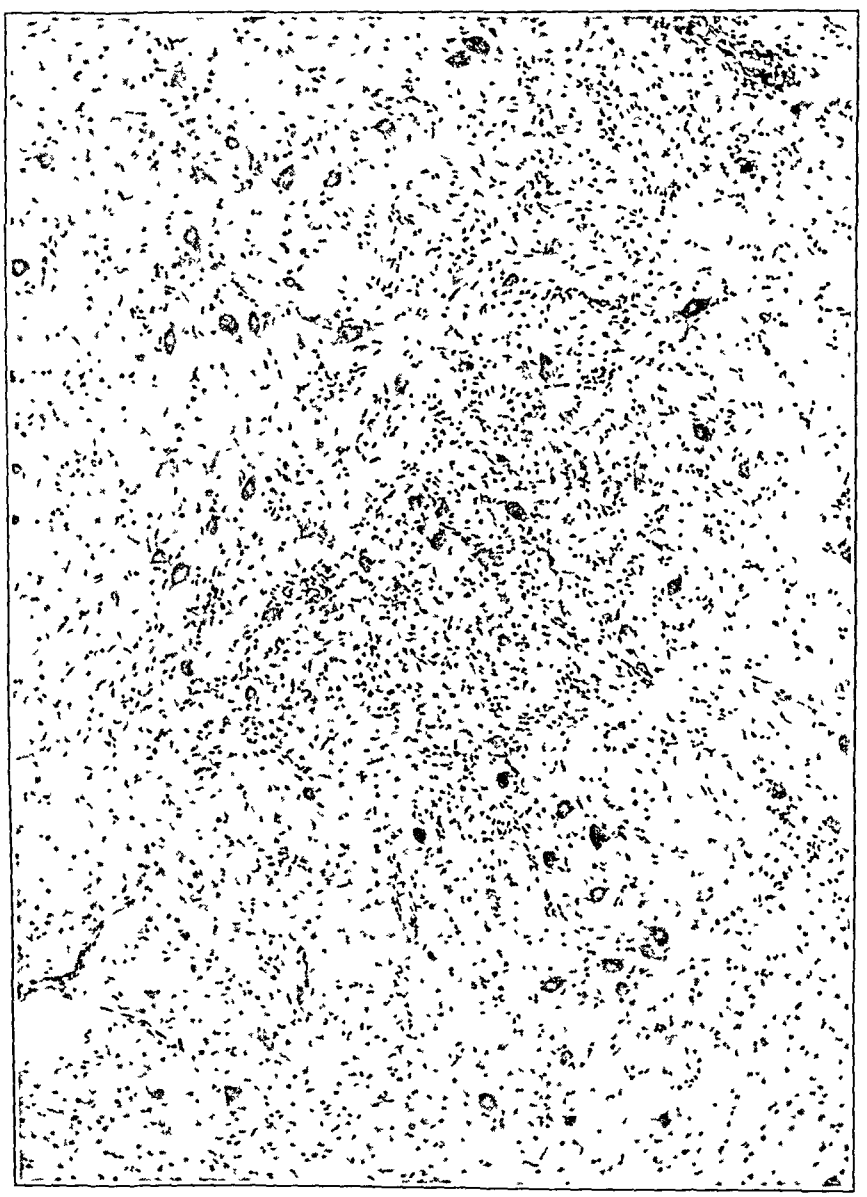


Fig. 5.—Tissue focus, showing glial and capillary hyperplasia and destruction of ganglion cells in the lateral cuneate nucleus of the medulla. Cresyl violet stain.

5. Bellavitis, A.: Nevrassite da herpes-zoster Contribute clinico-anatomico, Riv. di neurol. **4**:337, 1931.

6 Roger, H.; Poursines, Y., and Paillas, J.: Origine zostérienne probable d'une poliomésencéphalo-myélite subaigue, Rev. d'oto-neuro-opht. **16**:176, 1938.

7. Schiff, C. I., and Brain, W. R.: Acute Meningo-Encephalitis Associated with Herpes Zoster: A Fatal Case, Lancet **2**:70, 1930.

the right side of the lower jaw and the upper half of the neck and the occipital region on the same side. About a week later he became drowsy and confused and manifested bilateral ptosis and slight weakness of the lower right side of the face and of the right arm. The deep reflexes were absent; the plantar responses were normal. Examination of the spinal fluid revealed 120 mononuclears per cubic millimeter. The patient became comatose, the temperature remaining below 99.4 F., and died of bronchopneumonia twenty-one days after the onset of the preeruptive neuralgic pain. Two or three days before the patient's death his son, aged 32, became ill with chickenpox. The spinal fluid of the patient with herpes zoster gave a positive reaction in a complement fixation test when used as an antigen against the serum of patients convalescing from the disease.

Andre-Thomas and Buvat[8] described the case of a woman aged 58 who had been psychotic for several weeks, whereupon there developed herpes zoster of the trunk. With the appearance of the herpes the patient soon became comatose, showed rigidity of the neck (without, however, pleocytosis of the spinal fluid) and died at the end of the eighth day. Necropsy was not performed. The authors raised the question whether encephalitis may complicate herpes zoster.

8. Andre-Thomas and Buvat, J. B.: Existe-t-il une encéphalite zonateuse? Herpés zoster à foyers multiples (mort au huitiéme jour), Paris méd. **1**:600, 1931.

Castel[9] reported the case of a man aged 42 who had herpes zoster, with an eruption over the second to the fourth cervical dermatomic area on the right side. Lumbar puncture revealed 28 lymphocytes per cubic millimeter of spinal fluid. About twenty-three days after onset of the herpes there developed peripheral palsy of the right side of the face, which gradually cleared up. However, about forty days after the appearance of the herpes, crises of dysesthesia, provoked by slight contact, occurred on the right side, and examination revealed loss of position sense in the right extremities and stereoanesthesia of the right hand. A month later paresis of the right upper extremity associated with hyperflexia was noted. At the last examination, three months later, the subjective sensory disturbances and the astereognosis of the right hand (with preservation of ordinary tactile, topognostic and vibratory sensibility) were still present. In spite of lack of anatomic verification, the author expressed the belief that the clinical signs were indicative of a lesion of the thalamus of zosteric origin.

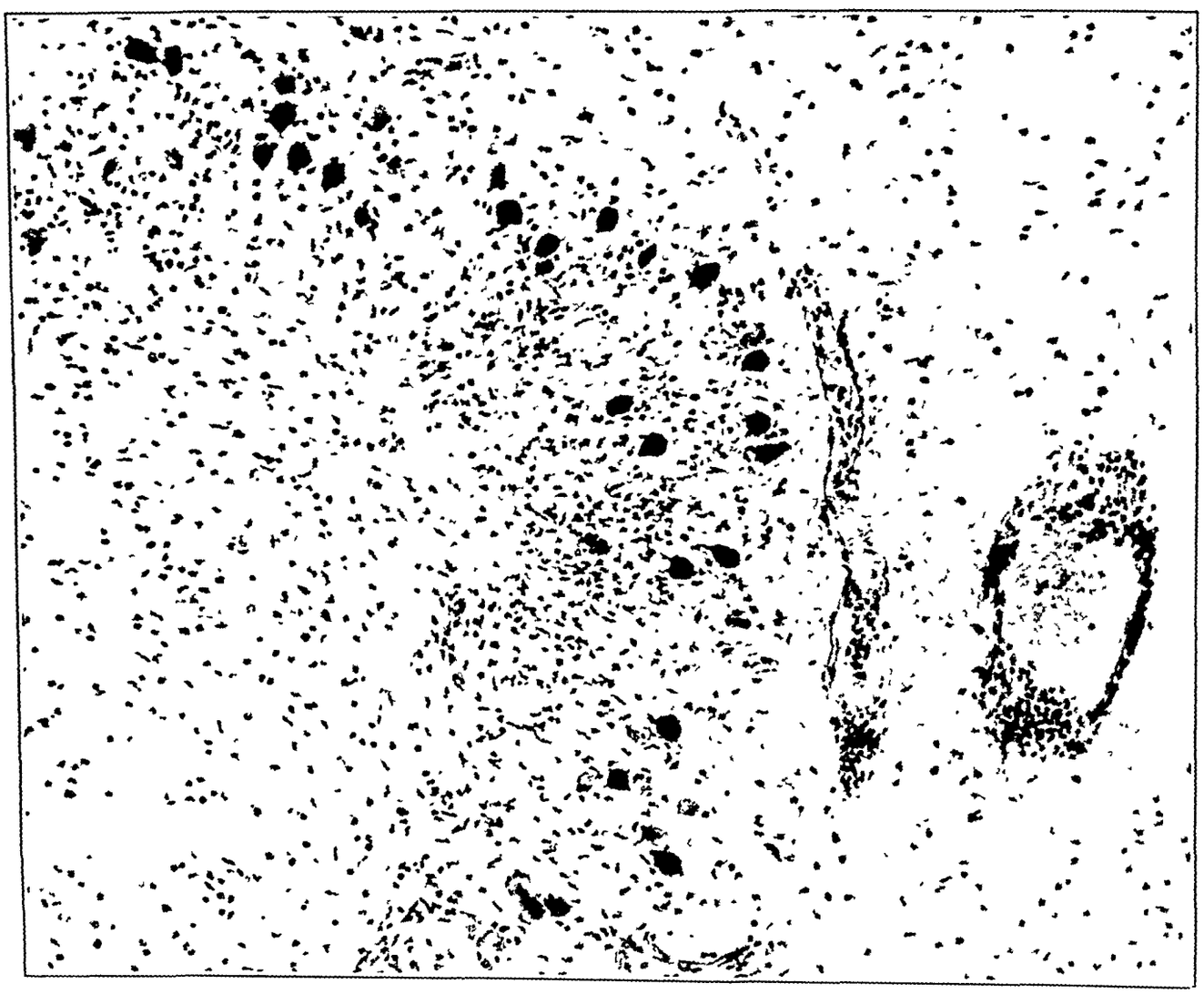


Fig. 6.—Tissue focus, marked particularly by glial hyperplasia, in the inferior olivary nucleus, with adjacent perivascular infiltration. Cresyl violet stain.

Certain similar features of the present case and of 6 cases[10] reported in the literature in

9. Castel, J.: Sur un nouveau cas d'atteinte du névraxe dans le zona, Thesis, Lyon, Bosc frères, 1935.

10. Thalhimer.[2] Biggart and Fisher.[3] Anderson and Wulff.[4] Bellavitis.[5] Schiff and Brain.[7] Andre-Thomas and Buvat.[8]

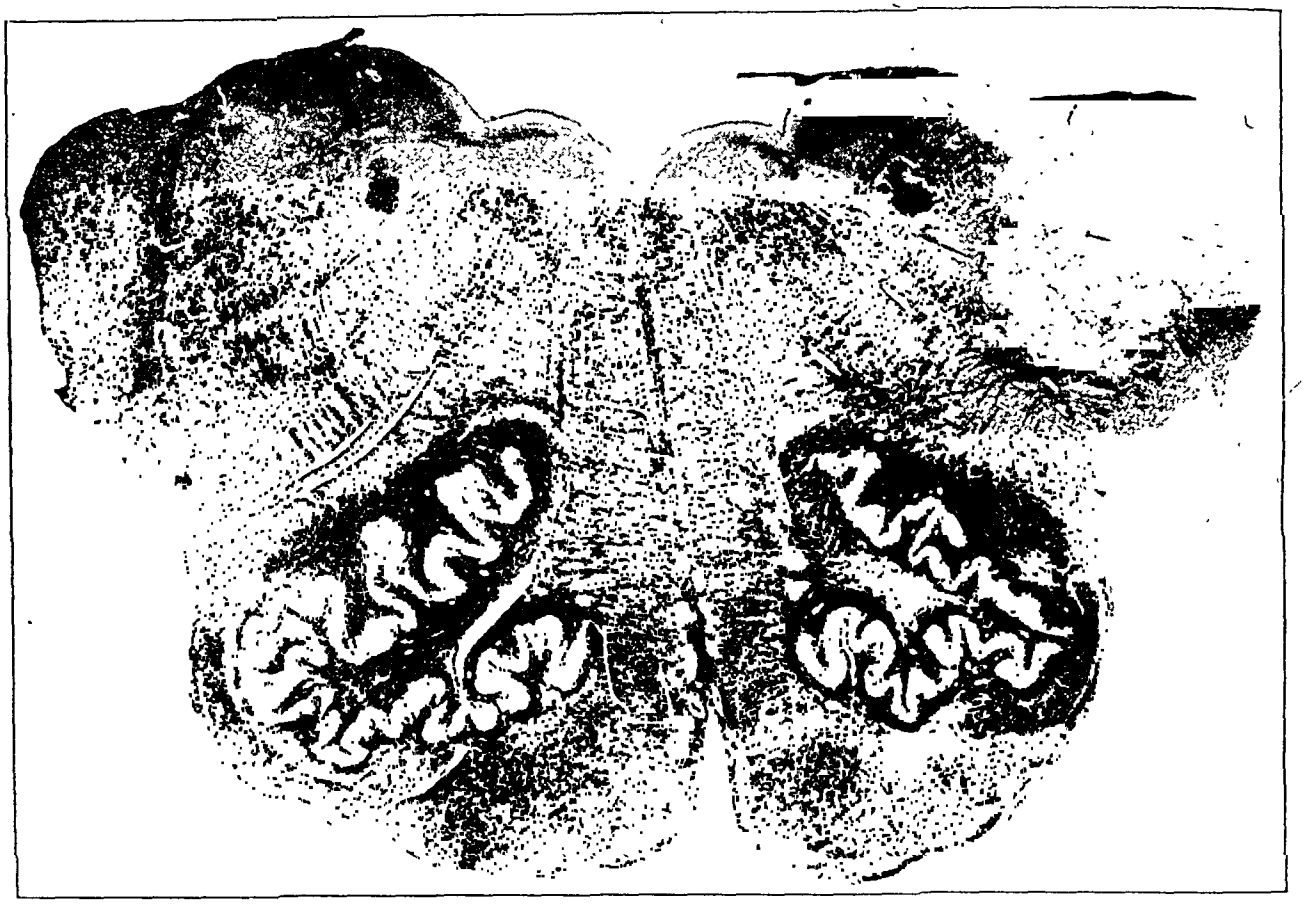


Fig. 7.—Low power view of the medulla oblongata, showing foci of destruction of myelinated fibers adjacent to one inferior olivary nucleus. Weil stain.

Fig. 8.—Small area of destruction of myelinated fibers adjacent to the inferior olive in the medulla. Weil stain.

which data are available are of interest. The dermatomic level of the cutaneous eruption was apparently cervical except in 1 case, that of Biggart and Fisher,[3] in which it was sacral. The interval between the onset of clinical herpes zoster and the symptoms of encephalitis was from four to six weeks in 3 cases in which the clinical manifestations were generalized (drowsiness, delirium or irrationality) and about one to three weeks in 4 cases in which the onset was with focal signs, such as facial palsy.

Herpes zoster has been noted to occur in the course of other neurotropic diseases. Thus, Netter [11] found that when herpes zoster and lethargic encephalitis occurred in the same patient, the zoster usually followed the encephalitis. In 3 of the cases reported by Netter some relation between herpes zoster and chickenpox was indicated because the latter disease developed in persons in contact with the patients.

The much discussed problem of the relation between herpes zoster and chickenpox is of some importance in this condition. Encephalitis following chickenpox is well known (van Bogaert,[12] Zimmerman and Yannet [13]) but is marked by perivascular infiltration and demyelination, especially in the cerebral and cerebellar white matter, without significant involvement of the brain stem or the cord.

SUMMARY

The amount of literature on encephalitis of presumed zosteric origin is meager but is sufficient to indicate that this complication may occur. The overflow of the herpetic inflammatory process to the efferent side of the neuraxis with facial palsy or myelitis has been well authenticated clinically. Meningitis as a complication of herpes zoster has also been clinically established. Until further cases have been carefully studied and reported, knowledge of encephalitis as a complication of herpes zoster must remain unclear. In previous cases in which necropsy was done the cerebrum, in contradistinction to the brain stem, was mildly involved by demonstrable infiltrative changes. In the present case there were no infiltrative changes in the neuraxis above the medulla oblongata, and it is suggested that the toxic encephalopathy affecting the brain proper may have been an allergic response to the virus of herpes zoster.

55 East Washington Street.
59 East Madison Street.

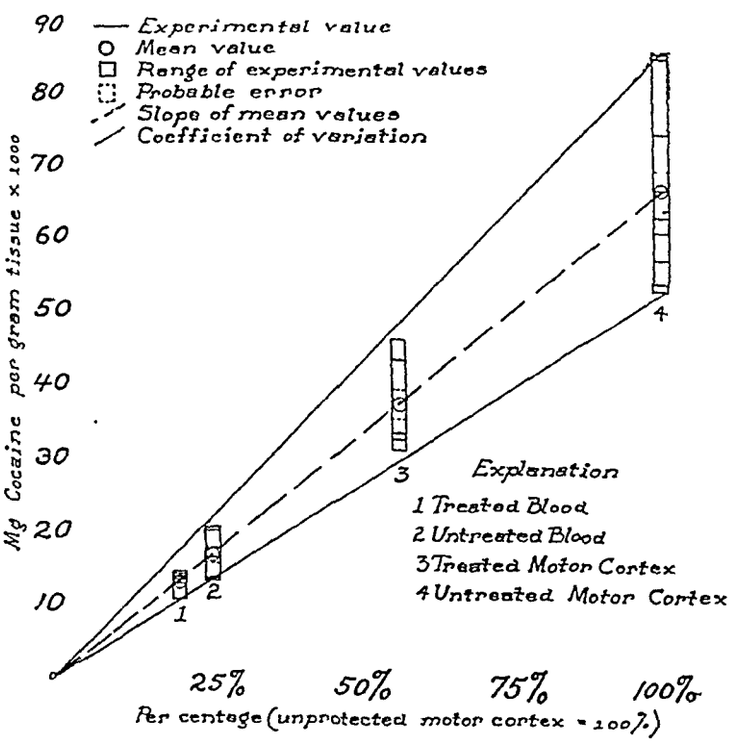
11. Netter, A.: Seize observations de zonas dans l'encéphalite léthargique, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:793, 1930.

12. van Bogaert, L.: Contribution clinique et anatomique à l'étude des manifestations neurologiques et psychiatriques de l'infection varicelleuse, J. de neurol. et de psychiat. **30**:623 (Oct.) 1930.

13. Zimmerman, H. M., and Yannet, H.: Non-suppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. **26**:322 (Aug.) 1931.

CORRECTION

In the article by R. B. Aird and L. Strait entitled "Protective Barriers of the Central Nervous System," on page 54 of the January 1944 issue of the ARCHIVES, figure 3, page 62, is not the illustration intended for that place. The correct graph is presented herewith. The legend for the figure as given in the original article is correct.



CHRONIC CHLOROFORM POISONING

CLINICAL AND PATHOLOGIC REPORT OF A CASE

GERT HEILBRUNN, M.D.; ERICH LIEBERT, M.D., AND PAUL B. SZANTO, M.D.
CHICAGO

Motivated by interest in a case of prolonged addiction to chloroform falling under our observation, an investigation of the relative frequency of this aberration disclosed only 29 authentic cases in the literature appearing after the discovery of this drug, in 1830, and its subsequent introduction into medical science.

Twenty-four cases were reported before 1900; only 5 cases have since been recorded.[1] In the majority of the accounts neurologic data were not included, the statements being limited to the cause of the addiction and the amount and mode of consumption. Of the authors, only Friedländer,[1a] Rehm [1b] and Storath [1f] offered a résumé of neurologic observations, in addition to somewhat more specific data pertaining to the physical status of their patients. Pathologic reports were not included in any of the records.

The use of chloroform in general was initially actuated by a painful minor disorder, such as toothache, neuralgia, dysmenorrhea, rheumatism or headache. In several cases the ailment persisted, and with it the use of the drug; in other cases resort to chloroform was continued although the original cause had long since disappeared. Without exception, the drug was consumed by inhalation, and only rarely by supplementary oral administration. Its use varied from three days to forty years, and the amount, from a few drops to 1,000 cc., taken within twenty-four hours.[2] Two cases reported by Svetlin (table) could not be tabulated as instances of chronic addiction to the drug, for the limited periods of consumption of three and thirteen days respectively did not represent gross use.

The consequences of abuse of chloroform varied from a completely negligible effect to "wrecking of the physical and mental energy of the patient"; on a lesser scale, the effect was described as irritability and a propensity toward moods of depression and anxiety. Delusions, hallucinations and delirious conditions were observed, as well as emaciation, paresthesias and tremor of the hands (table). It was uniformly emphasized, particularly in the more detailed reports, that withdrawal symptoms were not encountered. The authors invariably stressed the short duration within which withdrawal and "cure" could be effected but added that the patients had frequent relapses into the old habit.

REPORT OF CASE

History.—A white man aged 33, a bookkeeper, with a creditable work record, had been addicted to the use of chloroform for twelve years. He was described by his mother as considerate, with an even, tranquil disposition. Throughout the four years of high school he had maintained excellent grades.

The addiction began twelve years prior to his hospitalization, in 1940, when, at the age of 21, he had a rheumatic attack and was advised by a pharmacist to inhale chloroform for alleviation of the pain. Within three months the pain had abated, but the patient continued to take the drug each night in 1 ounce (29.5 cc.) doses for seven years and in 2 ounce (60 cc.) doses during the five years preceding hospitalization. In August 1939, at the close of ten years of addiction, the patient grew restless and worrisome and became easily excitable. He asserted that he slept with difficulty.

"To play a prank on a friend," he turned in a false fire alarm and was arrested. After a ten day stay in an institution, he abstained from chloroform for five months. It was learned that on his resuming the habit he frequently fell wherever he might be, lapsing into heavy slumber. He falsely asseverated at this time that he maintained twelve men under his industrial supervision and fictitiously asserted that a former friend, Dr. X, often called on him. He became depressed and wept freely, rejected food and grew increasingly careless of his appearance.

The patient abruptly abandoned the use of chloroform on Dec. 19, 1940 and had a convulsion three days later. At this juncture he was rehospitalized. Pronounced ataxia of his extremities and dysarthria then developed, manifestations which, according to the history and the patient's statement, had not been observed at any previous period. On December 28 he was transferred to the Elgin State Hospital. There, during the first

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1. (*a*) Friedländer, J.: Habitual Chloroform Abuse, Deutsche med. Wchnschr. **33**:1494, 1907. (*b*) Rehm, P.: Chloroform, Berl. klin. Wchnschr. **22**:317, 1885. (*c*) Schoenfeld, A.: About Chloroform Mania, Med. Klin. **28**:1272, 1932. (*d*) Toebben, H.: Chloroform Addiction in Connection with Other Morbid Desires, Deutsche Ztschr. f. d. ges. gerichtl. Med. **12**:285, 1928. (*e*) Clark, J. E.: A New Habit, M. Rec. **27**:452, 1885. (*f*) Storath: Habitual Chloroform Abuse, Deutsche med. Wchnschr. **36**:1362, 1910.

2. Meggendorfer, F.: Psychoses Due to Intoxications, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1928, vol. 7, pt. 3, p. 292.

few days, he conversed with imaginary persons and expressed the erroneous belief that his mother was in an adjoining room talking with strangers—an hallucinatory episode which cleared within ninety-six hours. Thereafter the patient remained in a friendly and cooperative mood, with commendable insight into his situation. For the remainder of the period of hospitalization overt psychotic symptoms were not discerned.

The vocabulary intelligence quotient on the Wechsler-Bellevue scale was 103; the Babcock efficiency index was determined to be —1.

On being interrogated as to his addiction, he answered that neither lustful sensations nor agreeable fantasies were associated with the use of chloroform and said that he indulged in the habit merely to insure a sound night's sleep.

Physical Examination.—The patient was slender and of small stature. His height was 5 feet 4 inches (162.5 cm.), and his weight 101 pounds (45.8 Kg.) (average weight, 125 pounds [56.7 Kg.]). The liver and spleen were without appreciable deviation from the normal. A loud, ringing apical first tone was observed. The blood pressure was 120 mm. of mercury systolic and 80 mm. diastolic; the pulse rate was 96 per minute.

Neurologic Examination.—Only the most significant findings will be noted. The pupils reacted to light and in accommodation. There was no nystagmus. The deep reflexes were normal. The abdominal and cremasteric reflexes were present. Cutaneous and deep sensibilities were intact. There was severe dysarthria, together with pronounced ataxic gait, coarse intention tremor of the tongue and fingers and manifest adiadokokinesis of the tongue and extremities. Romberg's sign was elicited with the patient's eyes open or closed. No hypotonia was present. Nystagmus and past pointing were elicited on rotation. Laboratory tests did not reveal anything pathologic. The spinal fluid was normal. A diagnosis of addiction to chloroform, with involvement of the cerebellar system and acute hallucinosis, was made.

In the next six weeks, under a dietary regimen of rich calories and vitamins, all neurologic symptoms appreciably diminished.

Data on Reported Cases of Chronic Chloroform Poisoning

Author	Year	No. of Cases	Daily Amount of Chloroform	Duration of Addiction	Psychiatric Symptoms	Neurologic Symptoms
Vigla [1a]	1867	1	30 Gm.	.....	"Impaired moral disposition"	
Boehm [1a]	1867	1	.....	.....	"Attacks of melancholia; ideas of persecution"	
Buechner [1a]	1867	1	.....	.....	"Periodic mania"	
Leudet [1d]	1874	1	150 cc.	10 yr.	.....	Paraplegia, which disappeared after a few months
Merie [1a]	1875	1	Every 5 days 1 lb. (373 Gm.)	.....	"Peculiar psychic behavior"	
Svetlin [1a*]	1882	1	.....	3 days	"Auditory, visual and sensory hallucinations"	Tremor; insomnia
		1	.....	13 days		
Watkins [1d]	1884	1	45 Gm.	15 yr.	"Hallucinations"	Tremor (delirium tremens)
Rehm [1a]	1885	1	Large amounts, sometimes 100 cc. in 24 hr.	Years	"Slowing of intellect; slight depression; weakness of memory"	
		1	.....	30 yr.	"Good memory and intellect, but severe deliria; suspiciousness"	
Schuele [1b]	1885	1	"Increasing amounts"	Many years	"Deliria; ideas of persecution; violence; irritability"	
Browning [1d]	1885	1	.....	Over 1 yr.	"Mental and physical wreck"	
		1	.....	5 yr.		
		1	.....	3 yr.		
		1	.....	8-10 yr.		
		2	.....	Years		
Clark [1d]	1885	1	½ pt. (236 cc.)	8 yr.	"Body and mental faculties affected"	Tremor
		1				
		3				
Connor [1e]	1885	1	.....	2 yr.		
Kornfeld-Bikeles [1a]	1893	1	15 to 20 Gm.	2 yr.	"Depressed mood"	Headaches; tremor of hands; narrow pupils; no reactions to light
Lewin [1d]	1897	1	.....	40 yr.	"Change of personality and temporary deliria"	
		1				
Schenzer [1c]	1904	1	.....	.....		
Friedländer [1a]	1907	1	20 drops	14 yr.	"Depression"	Left hemiplegia after 9 yr. of addiction, at age of 60; right hemiplegia 5 yr. later
Storath [1f]	1910	1	50 Gm.	15 yr.	"Stilted, manneristic behavior; superior intelligence"	Rheumatic pain; slight tremor of hands; no ataxia
Toebben [1d]	1928	1	20 Gm. several times a wk.	3 mo.	"Psychopathic personality; addicted to alcohol, cocaine, eucaine and procaine"	
Schoenfeld [1c]	1932	1	100 Gm.	15 yr.	"Quiet, calm, social"	

* These cases do not represent chronic addiction to the drug.

On March 2, 1941 diphtheria developed, with a temperature of 105.4 F. Forty thousand units of diphtheria antitoxin U. S. P. was immediately injected, and the patient's condition improved the next day. On that day 20,000 additional units was administered. In the afternoon the temperature rose again, from an early reading of 103 C., and, notwithstanding the administration of an additional 40,000 units, the patient died, on March 5.

Autopsy.—Autopsy, performed two hours after the patient died, disclosed severe toxic myocarditis as the immediate cause of death. Arteriosclerotic changes, either in the aorta or in the coronary vessels, were not noted. The liver was slightly larger than normal and weighed 1,515 Gm. Its firmness was moderately decreased, and the architecture of the cut surface was obscured. The spleen showed changes characteristic of sepsis.

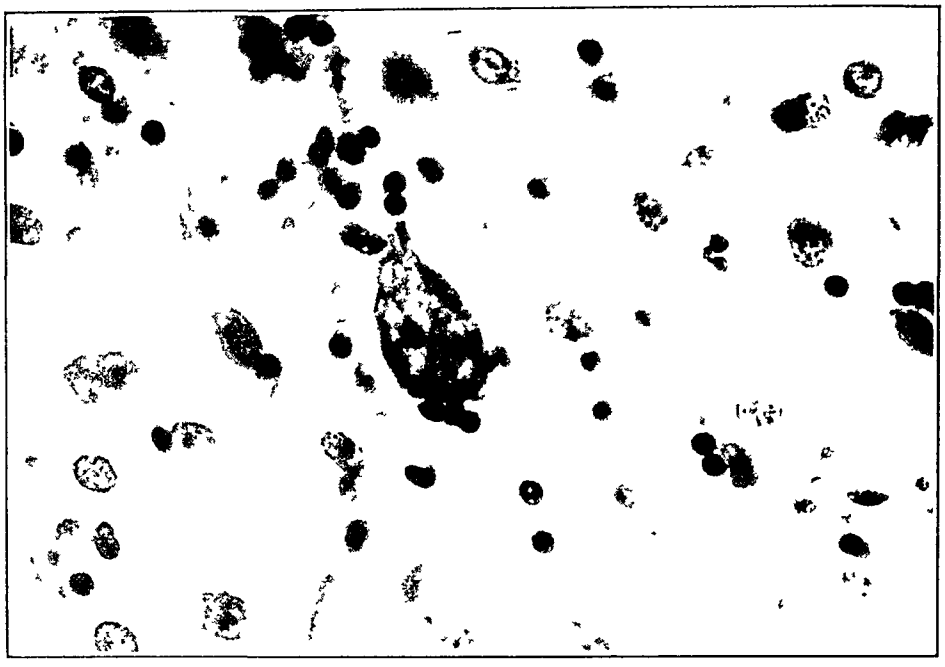

Fig 1.—Sections of the putamen, showing numerical reduction and shrinkage of the large ganglion cells

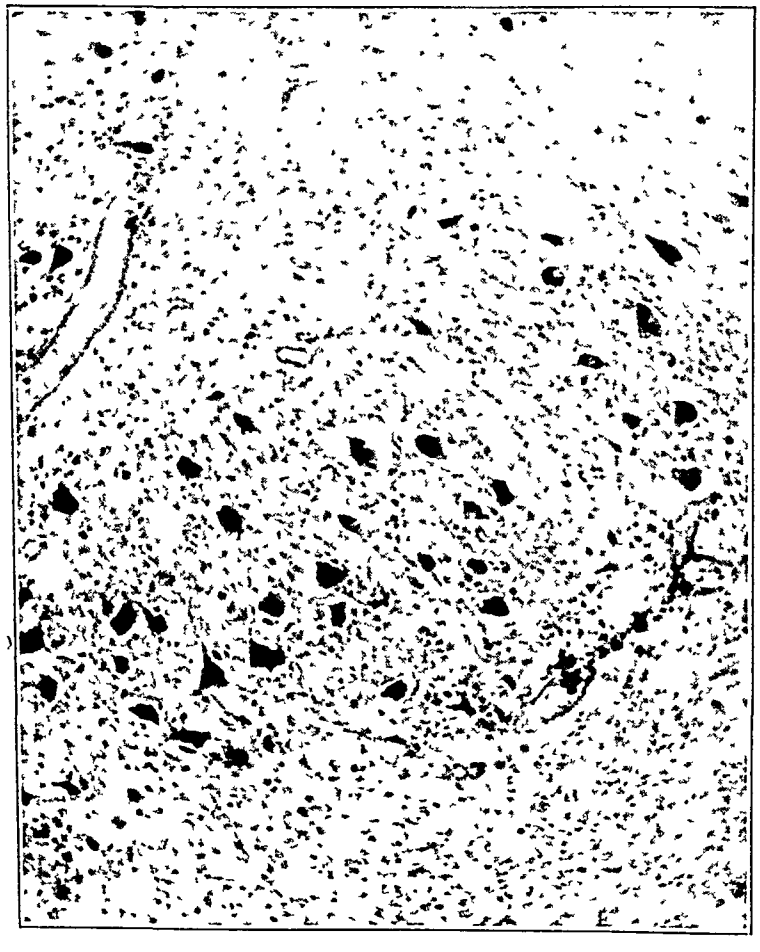

Fig. 2.—Dentate nucleus, showing numerical reduction of ganglion cells, acellular areas and shrinkage and shadow cell formation.

Microscopic Examination.—Liver: There was moderate increase of the periportal connective tissue, with round cell infiltration. The liver cells showed cloudy swelling, due to the acute infectious disease.

Brain: On removal of the brain, a negligible amount of clear cerebrospinal fluid escaped from the subarachnoid space. The meninges were smooth and glistening. The brain, which was of normal size, weighed 1,265 Gm. No evidence of localized atrophy or arteriosclerosis was observed; the basilar arteries were without essential change.

Coronal section immediately anterior to the temporal poles failed to reveal basic changes. Before the brain was fixed entire in a 10 per cent concentration of solution of formaldehyde U. S. P. several blocks were selected for frozen sections and Cajal preparations.

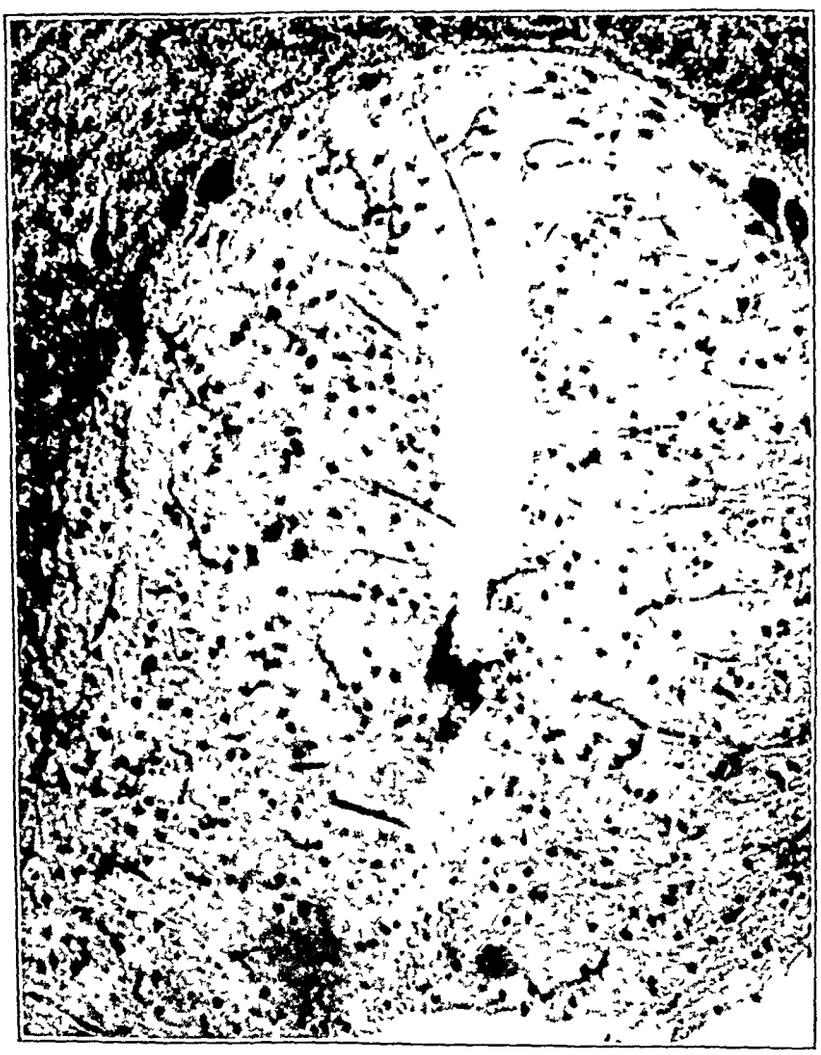

Fig. 3.—Cerebellum, showing numerical reduction of the Purkinje cells and moderate gliosis of the molecular layer.

Sections were taken for microscopic study from the various cortical areas, the basal ganglia, the cerebellum and the brain stem and stained with sudan IV and with the Nissl, Weil and Cajal methods. Additional Bielschowsky preparations were obtained from the cerebellar sections.

The frontal lobes presented slightly thickened meninges, with large numbers of fibroblasts and dilated blood vessels. The endothelial cells of the meningeal vessels were normal. In the perivascular spaces of the arterioles a few lymphocytes were seen in scattered fields, and the veins were moderately dilated. The architectonics of the frontal lobe was not disturbed. The large pyramidal cells in the third layer were essentially normal, except for a small number in which the nucleus was eccentrically located. In summary, a definite pathologic picture was not maintained. Examination of the remaining cortical areas yielded similar results.

The large cells in the putamen (fig. 1) had undergone numerical reduction. In many of these cells the nucleus was eccentrically located, with yellowish pigment of varying amount. The small ganglion cells were without pathologic involvement. The astroglia cells around the blood vessels were not increased. The oligodendroglia cells, which were slightly swollen, were moderately increased in number.

In the cerebellum, the most conspicuous changes were demonstrable in the dentate nucleus (fig. 2), with the cells showing moderate degenerative changes, manifested by shrinkage and poor staining quality and by reduction of their number in some fields. In certain areas the Purkinje cell count was diminished, and the number of glia cells in the molecular layer (fig. 3) was increased. Generally, however, the Purkinje and basket cells were well preserved. Bielschowsky preparations revealed that the fibers of the basket cells surrounding the Purkinje cells were unimpaired The brachia conjunctiva remained well myelinated.

Sudan IV stains disclosed accumulation of fat in the protoplasm of certain cells of the inferior olivary nucleus, the presence of which did not necessarily indicate pathologic change. The vessels and cells of the red nucleus appeared normal.

COMMENT

A man aged 33, who had inhaled 1 to 2 ounces of chloroform daily for twelve years, experienced

a fleeting psychotic episode, requiring a ten day period of hospitalization, after approximately ten years of addiction. In the eleventh year of his addiction he began to have frequent delusional ideas and auditory hallucinations. A convulsion in the twelfth year of the habit precipitated the final hospitalization, when the patient came under our observation. He was in an acute hallucinatory and delusional state, which cleared within four days, and he remained without overt psychotic symptoms for the rest of the period of hospitalization. Such manifestations as pronounced dysarthria, severe ataxia, dysdiadokokinesis and action tremor suggested disturbance of the cerebellar system. These symptoms, with dietary control, yielded striking improvement within a few weeks. He died of diphtheria.

Histologic examination of the brain revealed moderate changes in the putamen, characterized by the presence of yellow pigment (lipofuscin) in the large ganglion cells, which were numerically reduced. Similar changes were described by Carmichael and Stern [3] in the cortical ganglion cells in cases of chronic alcoholism. In certain areas of the cerebellum the Purkinje cells and the ganglion cells of the dentate nucleus showed moderate numerical decrease, with shrinkage and poor staining quality distinctly betraying the chronic character of these alterations. Of importance, however, was the absence of edema of the brain and petechial hemorrhages in the white matter—morphologic criteria for the effect of diphtheria toxin, according to Hall.[4] The absence of these changes affords grounds for dismissal of diphtheria as the cause of the visible damage to the brain.

The moderate pathologic changes in the putamen and the cerebellum do not assuredly constitute the morphologic foundation of the neurologic manifestations observed during the initial phase of the clinical period of observation. The subsidence of these neurologic symptoms appears to be commensurate with the paucity of histopathologic signs. From Bumke's [5] notation of "shrinkage and severe changes in the ganglion cells of a diffuse type throughout the central nervous system" in cases of death due to acute chloroform poisoning, an observation in contrast to the alterations in our case, it may be surmised that the histologic changes, despite the long duration of the addiction were reversible, analogous to lesions associated with chronic alcoholism or habitual barbiturate poisoning.

SUMMARY

A man with addiction to chloroform of twelve years' duration presented acute neurologic symptoms suggesting cerebellar involvement. After a diphtheritic infection, of which he died, microscopic examination of the brain disclosed unspecific moderate degenerative changes of the ganglion cells in the putamen and the cerebellum.

6500 Irving Park Road.

3. Carmichael, E. A., and Stern, R. J.: Korsakoff's Syndrome: Its Histopathology, Brain **54**:189, 1931.

4. Hall, W. E. B.: Diphtheria and Acute Toxic Encephalitis, with Report of Case, Canad. M. A. J. **26**:566, 1932.

5. Bumke, O.: The Anatomy of the Psychoses, in Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1928, vol. 11, pt. 3.

Obituaries

GRAEME MONROE HAMMOND, M.D.

1858-1944

The passing of Graeme Monroe Hammond in his eighty-sixth year signalizes an event in the history of neurology and psychiatry in New York, since there is now only one left of that generation who represented this district among the leaders of American neurology and psychiatry.

The last male of three generations of physicians, as well as the son of one of the pioneers in the field of neurology, young Graeme had an eager, acquisitive mind. He had the prescience to fortify himself with a scientific background by first studying in the old Columbia School of Mines, class of 1878, after which he turned to medicine and graduated from New York University Medical College in 1881. He must have felt an inclination toward neurology, for shortly thereafter he became a member of the American Neurological Association, which he served faithfully and ably as secretary-treasurer for many years and as president in 1898. Medicolegal practice interested the young neurologist to such an extent that he studied at the New York Law School, graduating with the degree of Bachelor of Laws in 1897.

In 1908 Dr. Hammond became a fellow of the American Psychiatric Association and showed by his discussions at the meetings of the association a keen interest in psychiatry. He also participated actively in the meetings of the New York Psychiatric Society, of which he had been a member for many years.

He was a good teacher, possessing the knack of presenting his subject in a way that held the attention of his students. He had the chair of neurology and psychiatry at the New York Post-Graduate Medical School from 1896 to 1920.

He was public spirited and responded to every demand made on his time. In the first world war he promptly joined the Army and did excellent work in examining volunteers. Later he headed the neuropsychiatric elimination board at one of the nearby training camps. Because of his declining strength, he had gradually withdrawn from all activities during the past few years. However, when volunteers for medical control services in air raid precautions were asked for, he was one of the first to answer the call, and well I remember him at a meeting in the Seventh Regiment Armory, ready to do his bit if called on.

Dr. Hammond was a firm believer in the principle that a healthy body makes a sound mind. He always kept himself in good physical condition by some form of exercise. He was for many years the captain of the fencing team of the New York Athletic Club, and every morning early he could be seen running a mile or so before breakfast. I believe he continued this practice until his eightieth year.

For some time we have missed his kindly, genial personality at meetings. He always brought a practical, sound, common sense point of view to whatever subject he was discussing and was always courteous but firm in maintaining the position he had taken. I doubt if he ever lost his temper during a discussion, and he was never known to be aggressively sarcastic or vituperative, although there was often a strongly humorous quality to his remarks which thoroughly deflated the bombastic claims of other speakers.

His kindly spirit and undaunted courage will always be fresh in the recollections of those who knew him.

EDWIN G. ZABRISKIE.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE DISTRIBUTION OF CHOLINESTERASE IN THE BOVINE RETINA. C. B. ANFINSEN, J. Biol. Chem. **152**:267. 1944.

By employment of single horizontal sections of the retina both for quantitative histologic analysis and for chemical study, it has been possible to determine the localization of the enzyme cholinesterase in the layers of this organ. The results indicate a predominantly synaptic localization of cholinesterase. This provides direct support for the current theory of chemical mediation of the nerve impulse. The usefulness of the retina as a test organ for the study of the general physiology of otherwise inaccessible components of the central nervous system is pointed out.

PAGE, Cleveland.

TEMPERATURE EFFECTS ON REFLEXES OF ISOLATED SPINAL CORD: HEAT PARALYSIS AND COLD PARALYSIS. M. O. DE ALMEIDA, J. Neurophysiol. **6**:225 (July) 1943.

De Almeida, in a study of the effects of variations in temperature on spinal reflexes in isolated preparations of the spinal cord of American and Brazilian frogs, found that the time of resistance of the reflexes formed curves with a maximum corresponding to a mean temperature. The position and value of this maximum depended on the climatic conditions to which the animal was accustomed. Between temperatures of 14 and 29 C. reflex exhaustion was permanent. Beyond this range, paralysis was produced by heat and cold. These types of paralysis were not due to impairment of conduction but resulted from paralysis of nerve centers by metabolic products which were ineffective at mean temperatures.

FORSTER, Philadelphia.

ELECTROENCEPHALOGRAM OF DECORTICATE MONKEYS. MARGARET A. KENNARD, J. Neurophysiol. **6**:233 (July) 1943.

Kennard studied the electroencephalogram of monkeys, obtaining electrical potentials from the cortex and the subcortical nuclei in decorticate and hemidecorticate preparations. The patterns for the cortex, the basal ganglia, the thalamus and the hypothalamus were characteristic for each area. However, each cellular complex influenced the other complexes. The electroencephalogram from the basal ganglia in a hemidecorticate preparation showed low voltage, 8 per second activity; only when the entire cerebral cortex was removed did spontaneous bursts of high voltage activity appear. The thalamic pattern presented, like that of the cortex, a component of medium rate, and occasionally records from the thalamus and the postcentral cortex were synchronous. Thalamic lesions altered the cortical pattern, especially in the postcentral areas. While the hypothalamus presented little activity, its ablation notably altered the cortical electroencephalogram. Partial ablation of the thalamus or the hypothalamus temporarily altered the cortical electroencephalogram, but only when both the thalamus and the hypothalamus had been ablated were the cortical potentials abolished.

FORSTER, Philadelphia.

SPONTANEOUS ELECTRICAL ACTIVITY OF THE THALAMUS AND OTHER FOREBRAIN STRUCTURES. R. S. MORRISON, K. H. FINLEY and GLADYS N. LOTHROP, J. Neurophysiol. **6**:243 (July) 1943.

Morrison, Finley and Lothrop studied the spontaneous activity of areas of the forebrain in cats. Spontaneous bursts of 5 to 10 per second waves similar to potentials seen in the cortex were obtained from various areas of the thalamus. These areas were chiefly those associated with the internal medullary lamina. Activity of this type was not observed in the relay nuclei. The authors conclude that areas of the thalamus have a tendency to produce spontaneous rhythmic bursts but that these areas may be under the control of a master area associated especially with the internal medullary lamina. Characteristic spontaneous activity was also recorded from other subcortical regions.

FORSTER, Philadelphia.

NOTE ON THE ORGANIZATION OF THE TACTILE SENSORY AREA OF THE CEREBRAL CORTEX OF THE CHIMPANZEE. CLINTON N. WOOLSEY, WADE H. MARSHALL and PHILIP BARD, J. Neurophysiol. **6**: 287 (July) 1943.

Woolsey, Marshall and Bard studied the tactile sensory area of the anesthetized chimpanzee. Cortical responses, induced by mechanical movements of hair over various parts of the body, were amplified electrically and visualized by the cathode ray tube. The authors found that the tactile sensory area of the chimpanzee was organized in the same way as that of the monkey. All segments of the spinal cord below the eighth cervical were projected to the cortex in their spinal sequence, whereas the cervical segments were reversed *en bloc*. Thus, in the cortical sequence there are two areas of segmental discontinuity, one at the trigeminal-cervical boundary and the other at the cervical-thoracic boundary. These regions coincide with the boundary lines separating Dusser de Barenne's face, arm and leg areas.

FORSTER, Philadelphia.

THE RELATION OF AREA 13 ON ORBITAL SURFACES OF FRONTAL LOBES TO HYPERACTIVITY AND HYPERPHAGIA IN MONKEYS. THEODORE C. RUCH and HENRY A. SHENKIN, J. Neurophysiol. **6**:349 (Sept.-Nov.) 1943.

Ruch and Shenkin studied the effects of ablation of area 13 of the orbital surface of the frontal lobes in 5 Macaca mulatta monkeys. Hyperactivity appeared as early as the first postoperative day and increased to a maximum in the third or fourth week. After

this period a decrease in activity was usually encountered, but in no instance did the animal return to its preoperative state. Striking behavior deficits were apparent at least in the first postoperative week and consisted in a reduction of emotional expression, with absence of the startle reaction and a decreased fear reaction. The authors could not confirm the observations of other investigators that distractibility occurs with lesions of this region. The hyperactivity was accompanied by only a slight increase in food intake and by loss of weight. Ablation of other areas (10, 11 and 14) of the frontal lobe failed to produce the symptoms resulting from ablations of area 13.

FORSTER, Philadelphia.

Psychiatry and Psychopathology

THE PSYCHONEUROSES IN MILITARY PSYCHIATRY. JAMES A. BRUSSEL and HAROLD R. WOLPERT, War Med. **2**:139 (Feb.) 1943.

Brussel and Wolpert review the case records of all psychoneurotic patients admitted to a large station hospital during the first nineteen months of its existence. The commonest psychoneuroses encountered were anxiety states, conversion hysteria and reactive depressions. The rate of admission rose sharply after the Japanese attack on Pearl Harbor. Most of the patients had a high school education or better. The patients complained most frequently of precordial pain, nervousness, abdominal pain, "stomach trouble" and headache. The history seldom included a record of a previous admission to an institution, civil offenses, overt marital or other sexual maladjustment, suicidal thoughts or actions or fears. Patients with anxiety states and conversion hysteria often had a history of the death of some member of the family from a chronic incurable disease. Histories of psychoses, parental discord, alcoholism and criminality in the family were rare.

The authors recommend that before a psychoneurotic soldier is discharged from the Army his relatives be informed as to the nature of his illness, the therapy required and where and how it can be obtained.

PEARSON, Philadelphia.

MAJOR STUDIES ON FATIGUE. R. R. SAYERS, War Med. **2**:786 (Sept.) 1942.

Sayers gives a comprehensive review of the causes and prevention of fatigue. Fatigue results in a decrease of working capacity, a physiologic state involving changes in organic function, the formation of the chemical products of fatigue and a feeling of tiredness. It may be caused by physical overwork, but more commonly it is produced by psychologic and environmental strains: Two types of fatigue are mentioned in the literature—one originates entirely in the central nervous system; the second develops partly in the central nervous system and partly in the active muscles. The former occurs commonly: the latter is infrequent.

Physical fatigue may be (1) temporary, a feeling of tiredness which passes after a short rest and permits the resumption of work without decrease in efficiency; (2) subacute, when the reserves of energy are depleted, or (3) chronic, the final stage of overwork, which may initiate a condition of ill health.

In order to do the maximum amount of work with the minimum amount of effort, there must be complete coordination of the muscular movements with respiratory and circulatory activities. If the respiratory and circulatory responses are exaggerated, there is a useless expenditure of energy. The energic use of muscles depends on the interrelation of three factors: (1) changes in the skeletal muscles by which energy is transformed into muscular movement; (2) adjustments elsewhere in the body which provide the muscles with oxygen and the required foodstuffs, and (3) the means by which the two previous factors are bound together. Sayers points out that there is a physiologic basis for fatigue. When a muscle is stimulated repeatedly, there is first a slight fall in the amount of the contraction, followed by a regular increase in its extent, which is brought about by the action of the chemical substances produced by the contractile process. Finally the contractions diminish until the muscle ceases to respond at all. This is the state of fatigue of the muscle. Human muscle is 21 per cent efficient. If the rest interval between contractions and the weight of the load are kept constant, the extent of the contractions decreases as fatigue sets in. If the interval between contractions is long enough, fatigue is not apparent. After complete fatigue has occurred, a very long rest is necessary for the muscle to recover completely; if after complete fatigue further efforts to contract the muscle are made, the length of the period of rest necessary to produce recovery is much prolonged.

The capacity of the muscle to perform work is diminished by conditions which depress the general nutrition; e. g., loss of sleep, hunger, anemia or mental activity. When the circulation is improved and the amount of food, particularly sugar, is increased, there is an increased capacity to do work. The total output of muscular force is greater with small than with large loads. Notable activity in one set of muscles diminishes the amount of work put out by other sets.

The site of fatigue may be in the receptors, in the neuron cell bodies or in the muscle itself, in the region of the end plates and muscle fibers. Some authorities believe that the accumulation of lactic acid does not produce fatigue; they regard the production of lactic acid as a physiologic process. In their opinion fatigue is due to lack of oxygen.

Fatigue produces reduced efficiency, increased tendency to accidents and ill health. A temporary tendency to the development of accidents may be the result of lack of skill or of fatigue. A permanent tendency to accidents occurs usually in neurotic or psychopathic persons. It is clear, however, that a reduction in the number of hours of work leads to a decrease in the rate and the total number of accidents. A person should not be asked to work more than eight hours a day, or forty-eight hours per week. Perhaps forty or forty-four hours per week would be better.

Amar has summarized the science of human labor in his four laws. 1. The expenditure of energy is in proportion to the effort of the muscular contraction, its duration and its degree. 2. The expenditure of energy required to perform a given amount of work diminishes in proportion as the rapidity of the contraction increases. 3. There are an optimum effort and speed for the performance of the maximum amount of work with the minimum amount of fatigue. 4. The speed with which the muscle returns to a condition of repose is in proportion to the rapidity with which its work has been performed.

Working conditions should be arranged under the governance of these laws; i. e., the work should be

so organized that the minimum waste in effort and materials may be obtained. When such a program is combined with other health and safety programs, the number of accidents is decreased. If compulsory physical training of the civilian population were in vogue, especially of young adults, there would be an increase in efficiency and a lessened number of accidents.

PEARSON, Philadelphia.

PSYCHIATRY IN THE NAVY. FORREST M. HARRISON. War Med. **3**:113 (Feb.) 1943.

This is an interesting survey of the psychiatric program in the medical department of the Navy. The incidence of mental disease is relatively low, while the invaliding rate is high. The psychoneuroses, of course, form the largest group of mental diseases. Hysterical paralyses are rare. Harrison describes the organization for the exclusion of the mentally unfit and points out that proper screening at the time of enlistment is doubly important because many psychoneurotic men try to enlist in the Navy, and are even sent by their physicians to enlist in order to obtain a cure for their neurosis. Careful exclusion of the mentally unfit is necessary, for the complex and demanding naval life tends to bring out inherent weaknesses in the personnel.

Naval medical officers receive special instruction in psychiatry, and the Navy also has a definite program for the procurement of trained reserve psychiatrists and psychologists. Invaluable aid is rendered by the American Red Cross, which forms the psychiatric social service of the Navy.

The psychiatric service is valuable also in classifying the enlisted and commissioned personnel according to mental characteristics and in relating special abilities to specific tasks, so that each man may be in the position of maximum usefulness.

One of the most serious problems facing psychiatry in the Navy is the development, maintenance and improvement of morale both in peace and in war.

PEARSON, Philadelphia.

PEPTIC ULCER AT FORT GEORGE G. MEADE, MARYLAND. CHARLES A. FLOOD, War Med. **3**:160 (Feb.) 1943.

On the basis of his experience with patients suffering from peptic ulcer whom he saw at a station hospital during the past year, Flood evolved a plan of management for such patients in the Army. Most recent inductees respond poorly to treatment, both symptomatically and roentgenologically, while soldiers of the regular Army, with many years' service, respond well because they are usually of stable personality. Delayed healing of the ulcer is due usually to an associated anxiety state.

PEARSON, Philadelphia.

ACUTE EMOTIONAL DISTURBANCES IN TORPEDOED SEAMEN OF THE MERCHANT MARINE WHO ARE CONTINUING AT SEA. SYDNEY MARGOLIN, LAWRENCE E. KUBIE, MARK KANZER and LEO STONE, War Med. **3**:393 (April) 1943.

This report is based on the study at one or more interviews with 40 seamen who had been on torpedoed ships but who had volunteered to ship out again in spite of whatever inner turmoil they had suffered. It was possible to make some tentative statistical correlations between the severity of the reactions to the catastrophe and the evidence of previous mental illness, the age, years at sea, type of work, marital status racial and natural origin, degree of alcoholism, type of ship and position of the sailor on ship at the time of the catastrophe. The authors summarize their results and draw the following conclusions:

1. Severe persistent reactions offer a poor outlook for ultimate recovery.

2. Pathologic alcoholism or a history of a previous psychiatric illness predisposes to the occurrence of severe and incapacitating reactions.

3. Severe reactions occurred with the highest degree of frequency among the Anglo-Saxon, Scandinavian and continental European members of the steward's department and with lowest frequency among the Latin-Americans and Negroes of the same department.

4. Persons in the age period of 45 to 60 seem to be especially susceptible to severe reactions.

5. There was a suggestion that severe reactions are less common among married seamen.

6. Severe reactions were surprisingly high among seamen from tankers.

7. There was surprisingly little correlation between the position of the seaman on the ship at the time of attack or the severity of the experience as a whole and the severity of the after-effects. This suggests that variations in the external situation play a lesser role in determining severe reactions than do deep-seated endopsychic factors.

The authors attempt to explain the difference in the severity of the reactions between the northern European races and the Latin-Americans and Negroes by pointing out that it is customary to force members of the two last-mentioned races into employment in the steward's department; therefore those employed there are a fair sampling of their races, while it is so unusual for men of the northern European races to seek this type of work that those who do so participate because of some endogenous psychologic quirk.

The authors were impressed by the following personality traits of the group. The men tended to be small in stature, thin, wiry, gnarled and underfed. They were fairly consistently friendly and grateful for the interest shown in them. They were better read than most of a comparable group of working men. A majority had gone to sea early in life, and their motivation seemed to be a strong, inarticulate need to get away from home and the disciplined social authority and regimentation of life on land. This was so strong as to approach the status of a land phobia. More than half of the men were single, divorced or separated from their wives. Overtly, the majority were predominantly heterosexual, but the heterosexuality ranged from promiscuous relations with prostitutes to intense transient attachments to some kindly mother figure.

There was a hungry quality to the yearnings expressed which was often in poignant contrast to the history of rebellion against home and to the compulsive pattern of runaway lives.

Their political, social and economic attitudes were as divergent as could be found among any group of men. They were intent on service in the war effort and had a striking sense of loyalty to and pride in their union. Their independence and self sufficiency made them prickly toward the additional disciplinary and quasimilitary relations between the officers and men due to the exigencies of war. They were acutely

sensitive to the manner of their reception in foreign ports. They resented the inattentiveness of the British, which they contrasted sharply with the friendliness with which they were received in Russian ports. Bitterness in any form was rare, and in general criticisms were elicited only after considerable questioning.

PEARSON, Philadelphia.

MORALE. LEONARD R. SILLMAN, War Med. **3**:498 (May) 1943.

Sillman points out the need for the emotional conditioning of American soldiers for the battle situation. He believes that the soldier should be presented with a clear decisive formulation of why he has been placed on the battlefield and why he must conquer or die. Such a formulation should be combined with a slogan. Every technic possible should be used to get him to embrace this formulation passionately. Of course, such measures will stir deep emotions of hate and revulsion against the enemy, but this is necessary to give the soldier the psychologic resources necessary for the successful prosecution of the most harrowing experience of life, namely, war. Psychiatrists have found that soldiers who enter a campaign out of conviction suffer much less from war neurosis than those who do not.

Sillman points out that the American war effort cannot afford to continue to ignore the knowledge which psychoanalysts and psychiatrists have about anxiety, panic, aggression, submission, death, fears, etc.

PEARSON, Philadelphia.

AMBLYOPIA IN HYSTERIA. VINCENT P. MAHONEY and WILLIAM O. LINHART, War Med. **3**:503 (May) 1943.

Mahoney and Linhart studied 13 patients with hysterical amblyopia, whose cases they classified under (1) the acute, (2) the chronic and (3) the mixed form. Psychobiologic studies revealed that they were constitutionally immature, emotionally defective, resigned to their fate and poor in intellectual endowment. The predominating symptom in this series was referable to the visual apparatus. With 1 exception, all the patients gave lifelong histories of poor vision, beginning in the first three grades of school. Perimetric examinations showed concentrically contracted visual fields in all cases. The authors conclude that men with this form of amblyopia should not be inducted. When they are discovered in the armed services, they should be referred to a psychiatrist for disposal.

PEARSON, Philadelphia.

Treatment, Neurosurgery

RADIOGRAPHIC CONTROL FOR PARAVERTEBRAL INJECTION OF ALCOHOL IN ANGINA PECTORIS. JAMES C. WHITE and ROBERT W. GENTRY, J. Neurosurg. **1**: 40 (Jan.) 1944.

The results of paravertebral infiltration of procaine and alcohol in the treatment of intractable angina pectoris is satisfactory if the upper three or four thoracic ganglia and their rami are thoroughly impregnated. In 85 per cent of a series of 20 cases reported by White and Gentry good results were obtained by following the indicated technic. The chief difficulty lies in the accurate insertion of the needles, especially in the upper two ganglia. This difficulty has been overcome by checking the position of the needles after they have been inserted, by means of a portable x-ray machine.

WHITELEY, Philadelphia.

CEREBROSPINAL RHINORRHEA: SURGICAL REPAIR. WILLIAM J. GERMAN, J. Neurosurg. **1**:60 (Jan.) 1944.

Cerebrospinal rhinorrhea is said to be a relatively common complication of craniocerebral injury in the frontal region. Spontaneous recovery may occur as late as eight weeks after the injury, and the condition may develop after an interval of several weeks. In cases of the chronic condition surgical repair is always advisable.

German describes a method of repair which has been employed successfully for the past five years. It utilizes a dural flap from the crista galli to cover the defect in the cribriform plate. The author reports 5 cases in which this procedure was used with success. Medication with sulfonamide compounds is given for an appropriate period before and after operation. There were no recurrences of the rhinorrhea, and in only 1 case did meningitis (sterile), with mild fever and pleocytosis, develop.

WHITELEY, Philadelphia.

THE CHEMOTHERAPY OF INTRACRANIAL INFECTIONS: IV. THE TREATMENT OF PNEUMOCOCCAL MENINGITIS BY INTRATHECAL ADMINISTRATION OF PENICILLIN. COBB PILCHER and WILLIAM F. MEACHAM, J. Neurosurg. **1**:76 (Jan.) 1944.

Meningitis was produced in several groups of 10 to 14 dogs each by injection of type I pneumococci into the cisterna magna. Half of each group of animals were treated with penicillin, and the remaining half were used as controls. A total of 96 experiments were performed.

In the first series (48 experiments) 50 units of penicillin was injected intrathecally daily, with slight, but definite, improvement as compared with the condition of the untreated controls. In the second series, of two groups of 12 dogs each, doses of 100 and 200 units of penicillin respectively were injected intrathecally daily; almost half the treated animals survived, and most of the deaths were due to lobar pneumonia. Because of the resulting pneumonia, a third series (24 dogs) were treated with the intrathecal injection of 200 units of penicillin daily and the intravenous injection of 1,000 units three times daily; the results were even more favorable than those in the second series.

WHITELEY, Philadelphia.

THE USE OF PRODUCTS PREPARED FROM HUMAN FIBRINOGEN AND HUMAN THROMBIN IN NEUROSURGERY. FRANK D. INGRAHAM and ORVILLE T. BAILEY, J. Neurosurg. **1**:123 (Jan.) 1944.

Ingraham and Bailey discuss the progress made in solving two important neurosurgical problems: hemostasis and the prevention of meningocerebral adhesions. Fibrin foam has been developed as a hemostatic agent. It is a dull, porous material, slightly brittle, which in the dry state is composed of dense strands of fibrin fibers with air spaces, which may easily be seen with the naked eye. At the operating table the dry matrixes are soaked in a solution of human thrombin and are then applied to the bleeding surface. This application is instantly effective in hemostasis, whether with simple surface bleeding or with bleeding from deep venous channels. The advantages of the procedure are chiefly two: first, the shortening of many neurosurgical pro-

cedures and, second, the facilitation of many operations which had heretofore been impossible or too difficult because of profuse bleeding or diffuse distribution of the lesion. Histologic studies in human and animal experiments have proved that the foam is rapidly absorbed, with minimal or negligible tissue reaction, even in conjunction with the employment of sulfadiazine and penicillin.

The authors discuss, also, the use of a substitute for the normal human dura mater-fibrin film: This substitute is a strong, smooth, translucent, uniform, sheet with considerable elasticity. There are two principal uses for such a substitute: first, in the plastic repair of dura mater removed either by trauma or by operation and, second, in the prevention of meningocerebral adhesions, an important factor in posttraumatic convulsions. After animal experiments revealed the absence of tissue reaction, the absence of adhesions, the retention of the subdural space and the replacement of the film by a neomembrane of fibrous tissue, studies on human subjects were begun. Fibrin film has been removed at second operation or at autopsy at intervals varying from fourteen hours to eighty-one days; in no case was there any inflammatory reaction or evidence of adhesions. Concomitant use of sulfadiazine and penicillin did not result in any change in tissue reactions.

The authors conclude that, on the basis of present evidence, fibrin film is superior to other materials previously tested.

WHITELEY, Philadelphia.

Society Transactions

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

GERALD R. JAMEISON, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Feb. 8, 1944

Disturbances in Sleep Mechanism: A Clinicopathologic Study.

DR. CHARLES DAVISON and CAPTAIN EDWIN L. DE MUTH (by invitation).

Disturbances of sleep, consisting of insomnia or hypersomnia, may be divided into two main groups: disorders associated with lesions of the nervous system and psychogenic disorders. Attempts at correlation of this mechanism on a neuroanatomic and physiologic basis in man have led to various interpretations. The problem is beset with many difficulties because the lesions in many of our cases, and in cases reported by other authors, were neither isolated nor limited to specific areas in the nervous system. This is especially true of cases of somnolence associated with cerebrovascular and other diseases with bilateral or multiple lesions of the central nervous system. The localizing area responsible for this physiologic deviation may be determined with difficulty, even in cases of a single neoplastic lesion, because the growth may cause widespread disturbance in function through compression of other structures or through interference with the cerebrospinal circulation. A careful evaluation, however, of the clinical symptoms and the location of the significant lesion may help in a reconstruction of the localizing area and the important centers and pathways responsible for hypersomnia or insomnia.

As will be demonstrated, disturbances in sleep may occur with lesions at various levels in the nervous system, from the cortex to the medulla oblongata. There is experimental evidence indicating the possible location of these lesions in man. Although the hypothalamus seems to be the chief center controlling this function, it is well to remember that by means of its pathways the hypothalamus is in intimate connection with the cortex, the thalamus, the basal ganglia, the mesencephalon and the brain stem. A lesion in any of these centers or along their hypothalamic connections may account for the disturbance in the sleep mechanism. The disintegration of this mechanism may be caused by either destructive or irritative lesions or by psychogenic factors. Psychologic disturbances most likely depend also on interference with the centers and pathways to be described.

From the nosologic point of view, disturbances in sleep should include the various designations used, such as lethargy, somnolence, stupor, coma and unconscious states. Some observers have expressed the belief that these states are separate entities instead of various phases or stages of the same disturbance, regulated by the same centers and the same pathways. They have asserted that hypersomnia or somnolence should be differentiated from stupor, for the patient can be easily aroused from the former and when so aroused appears to be in complete possession of his senses.

Approximately 300 cases of disturbances in sleep mechanism were studied clinically, and autopsy was performed in 50 cases. In most of these cases the disturbance was the result of a neoplasm; in other cases a vascular or other disease of the nervous system was the causative factor. The cases, however, are described as far as possible in accordance with the location and the level of the lesion.

Level of Lesion	No. of Cases
Cortical	8
Corticodiencephalic	20
Diencephalic (hypothalamus)	17
Mesencephalic-metencephalic	5

A number of cases of diffuse lesions in the cortex, diencephalon, mesencephalon and metencephalon are omitted from this presentation because they would be confusing from the point of view of localization. The case of a patient with narcolepsy in which electroencephalographic studies were made illustrates the importance of the psychologic factors in the sleep mechanism.

In every case reported observations were made during the period of sleep disturbance. A number of questions were asked and attempts made to arouse the patient, as indicated in the brief history of each case. The few cases in which the patient was in deep coma and could not be aroused are not included in this presentation. As increased intracranial pressure, endocrine disturbances, ocular manifestations and other features have been claimed by some observers to play a role in sleep disturbances, special attention has been given these factors in the evaluation of their importance.

Illustrative cases from each group are presented. From the analysis of our clinicopathologic material, the cases reported in the literature and the results of animal experimentation, it is possible to reconstruct in part the centers and their connections which regulate the sleep mechanism, despite the insufficient evidence for some of the hypothalamic pathways. A neuroanatomic and neurophysiologic review of the subject is presented.

Although the evidence indicates that the hypothalamus is undoubtedly one of the chief centers for the control of sleep or wakefulness, other centers have to do with this mechanism. Our cases of diseases of the cortex and mesencephalon demonstrate that these structures must be in intimate connection with the hypothalamus and with other centers for the regulation of sleep. Interruption of these pathways to and from the hypothalamus may lead to interference with the same mechanism.

Narcolepsy as a Psychogenic Symptom.

DR. LEO A. SPIEGEL (by invitation) and DR. C. P. OBERNDORF.

A housewife aged 50 had had attacks of uncontrollable sleep for two years. These attacks were of variable duration; some lasted only a few minutes and others many hours. They were preceded by polydipsia and were frequently accompanied by cataplexy. At first a lesion affecting the hypothalamic area for sleep was considered, but psychiatric investigation revealed that the patient's condition belonged to the group of hysterical narcolepsies. The etiologic background for her symptoms was a complex, intrafamilial sexual relation-

ship, which began at the age of 6 years and was maintained for forty years. Solely by means of the cathartic procedure, as originally described by Freud, it became possible to rid the patient of her attacks of compulsive sleep, cataplexy and polydipsia. The disappearance of her narcoleptic attacks was followed by a profound sense of guilt, an occurrence suggesting that the function of the attacks of sleep was to allay this sense of guilt. From the point of view of therapy it is suggested that in selected cases the simpler methods of the early days of psychoanalysis may be more fruitful than the complex methods of modern psychoanalysis. The induction of sleep in this patient through the recall of traumatic memories and its dissipation through catharsis suggest the physiologic processes of inhibition and disinhibition, as described by Pavlov.

DISCUSSION ON PAPERS BY DR. DAVISON AND CAPTAIN DE MUTH AND BY DR. SPIEGEL AND DR. OBERNDORF

DR. SAMUEL BROCK: Dr. Davison and Captain De Muth have presented an excellent survey of the neuroanatomic and neuropathologic observations in cases associated with disturbance in the sleep mechanism. They have attempted to evaluate the various views relating to the parts played by the different segments of the central nervous system in this complex function. The authors have spoken of a voluntary control of the sleep mechanism by the cortex. With this I take partial issue. Sleep is essentially uncontrolled by the will, and while one may prepare oneself for sleep, one cannot speak of voluntary control without a good deal of reservation. Sleep is essentially a complex vegetative phenomenon, and the governing mechanism, I believe, is not the cortex but, rather, diencephalic and mesencephalic centers, in which are concentrated many other vegetative functions. The fact that certain drugs may induce sleep or wakefulness in thalamic and decerebrate animals indicates without question that the lower vegetative centers are the controlling agencies under physiologic conditions. That other parts of the central nervous system, such as the cerebral cortex, suffer modification or extinction of function is obvious.

Until recently there has been little insight as to how such a mechanism, situated in the diencephalon and the mesencephalon, can bring about sleep. Perhaps a clue is afforded by the work recently done on cerebral concussion. The unconsciousness brought about by injury to the brain has points of resemblance to sleep. In fact, Geoffrey Jefferson, the English neurosurgeon, speaks of traumatic unconsciousness as "parasomnia." Jefferson also stresses the part played in this condition by lesions in the region "extending caudally from the upper half of the fourth ventricle to the hypothalamus cephalad."

Some of the members of these societies may have heard Dr. Earl Walker, of Chicago, in December 1943, when he presented evidence to the effect that posttraumatic unconsciousness in animals is associated with extinction of cortical function, as revealed by electroencephalographic studies (Diagnostic Value of Electroencephalography, ARCH. NEUROL. & PSYCHIAT. **51**:203 [Feb.] 1944). May one not speculate on the possibility that the large correlation center, described by various authors, acts as an "electrical extinguisher or modifier," controlling and affecting widespread areas of the cortex and other parts to produce this remarkable phenomenon called sleep? Of course, inhibition in this sense, and on such a widespread scale—rhythmic in tempo, delicate in its response to various internal stimuli and external effects—is a phenomenon that still requires a great deal of study.

In disease, more especially in the narcoleptic-cataplectic syndrome, remarkable dissociations occur in the various elements making up sleep. Perhaps the most remarkable of these dissociations is the cataplectic deposturing produced by emotion. This represents the physical component of sleep dissociated from the mental and is accounted for by loss of function in lower centers. Indeed here, again, one has support for the view that thalamodiencephalic and mesencephalic mechanisms are the main activators of sleep and wakefulness, to which other parts of the central nervous system are subservient.

The remarkable case report presented by Dr. Spiegel and Dr. Oberndorf is difficult to discuss in a short period because of its many implications. The narcolepsy exhibited by the patient was seemingly conditioned by psychogenic factors. Yet one is beset by two pressing questions: Why did the patient make use of this particular, rare, conversion phenomenon, instead of using the much more common forms of paralysis? Why did the symptoms begin so late in life, i. e., at the age of 48, since the psychogenic factors went back many years? One wonders whether there was not a structural determinant in the diencephalon, since the patient exhibited other vegetative phenomena referable to nearby centers, such as polydipsia and pallor. This, of course, might lead to a formulation of the clinical picture as one compounded of psychogenic factors and an organic substrate. There can be no doubt that the usual idiopathic narcoleptic-cataplectic syndrome is an organic disease, since various observers have described oculomotor paralysis with diplopia and the Babinski toe sign during the seizure. Perhaps one seldom sees cases like the one described because the combination of psychogenic factors and adequate organic background is rare.

DR. S. P. GOODHART: Dr. Brock has ably discussed the localization and nature of the mechanism of sleep, with especial reference to its neurophysiology. The authors of the papers are highly qualified to discuss the psychosomatic relationships and are identified with studies both in organic pathology and in dynamic psychology. The relation of psyche to soma has given rise to many theories with respect to brain and body function. It was Hippocrates who first maintained that the brain is the seat of the mind, the source of intelligence, of volition and of bodily activity.

Dr. Davison's paper is a highly concentrated discussion of both physiologic and pathologic sleep. He speaks of the psychogenic and the organic basis of narcolepsy; this at once raises the question of what constitutes organic and what psychogenic.

As to the location of the sleep mechanism, clinical and pathologic investigations by Davison and others make it clear that because of the relations of nerve tracts and nerve centers to each other, both anatomic and physiologic, precise localization is speculative. Studies of large series of cases by Davison and others, including the cases which Dr. Davison presented this evening, confirm the fact that even fairly discrete lesions do not always permit functional interpretation. His series of cases, like many reported in recent literature, indicate that the disturbances of sleep may result from lesions at various levels, from the cortex to the metencephalon. The frontal lobe seems to have a definite relation to the physiology and pathology of sleep. I have seen neoplasms of the frontal lobe the initial symptom of which for a long period was a striking tendency to somnolence.

There are indeed many theories as to the mechanism of normal and pathologic sleep. The one that strongly appeals to me is that of Pavlov, who regarded sleep as a series of conditioned reflexes dependent on cortical control and cortical inhibitions. There is convincing evidence that the hypothalamus and the periventricular region of the third ventricle have a definite relation to sleep; I believe it to be an automatic center, so to speak, but I feel that the mechanism of the cortex and the anatomic connections with the diencephalon are the sources of physiologic production of sleep, both in its normal and in its pathologic manifestations. I cannot agree with Davison and the authors who maintain that stupor and coma, levels of unconsciousness, are phases of what is called the sleep mechanism. These pathologic conditions, especially the states resulting from trauma, have, in my opinion, little if any relation to normal sleep.

There is something to be said for the theory propounded by Ramón y Cajal, who expressed the belief that ameboid movements of the dendritic elements of cortical cells and transcortical fibers may be the determinants in the production of sleep; according to this theory, contact is established and broken by these physical movements.

The presentation by Dr. Spiegel and Dr. Oberndorf is an excellent and thorough study. The authors, wisely perhaps, have not given all the sordid details and the bizarre sexual perversions that doubtless were of etiologic influence in the development of this unusual clinical picture. The case offers subtle problems in psychosomatic relationships. In my opinion the case is not one of true narcolepsy, in the strict sense in which that term is used, nor do I feel that the clinical signs are entirely psychogenic. I prefer to speak of narcoleptiform seizures; neither the age of the patient nor the length of the individual attacks conforms to the usual brief or momentary periods of sleep seen in cases of true narcolepsy. There is much in the history of this case to suggest an organic change in the periventricular area of the third ventricle. The extensive nevi of the body, suggesting the presence of neurofibroma; repeated polydipsia, vomiting and headache over an extended period; prolonged attacks of somnolence from which the patient could not be aroused—all these suggest an organic pathologic process. The unquestionable psychogenic influence, as shown by the characteristic hemisensory syndrome, was, without doubt, a dominating influence in many of the symptoms. The authors of the paper apparently consider the entire picture psychogenic.

Of the therapy used, hypnosis seems to be of value in bringing out the amnesia and the dream content, and on this effect—the authors base their procedure in the long-continued application of catharsis, as outlined by dynamic psychology. It would seem that in this case hypnosis touched only the surface and did not reach the deep psychologic makeup of the patient so that she could handle her own situation and thus become conscious of, and reconciled to, her past experiences. I recall a case at Montefiore Hospital in which the hypnosis brought about a restoration, although it was only temporarily maintained; the patient might well have been permanently cured had psychoanalysis followed hypnotic therapy. The young man presented a postencephalitic parkinsonian syndrome, with the characteristic facies, salivation, suppression of normal associated movements, rigidity and tremor; because of certain other physical signs, however, my associates and I suspected a psychogenic influence. While the patient was under hypnosis and subsequently the signs and symptoms disappeared. All therapeutic measures were discontinued for three weeks, and the patient lapsed into his former pathologic state. The case raises many questions of the relation between psyche and soma and between the functional and the organic.

DR. CHARLES DAVISON: I wish to thank Dr. Brock and Dr. Goodhart for their discussion. I must disagree, however, with Dr. Brock about the volntary control of sleep. I believe, and he will agree with me, that sometimes, especially in emergency situations or during emotional strain, one can go to sleep or keep awake as one wishes. There are numerous illustrations, for instance, the marathon dancers who manage to keep awake for hours at a stretch in order to perform their act. Soldiers have been known to remain awake for two to three days or longer when required. Then there are the historical instances, such as those of Caesar, Napoleon, Goethe and Freud, who could go to sleep or keep awake voluntarily. Our first group of cases, in which there was cortical involvement, illustrates that the cortex is the representative for the voluntary control of the sleep mechanism, the chief center of which is situated in the hypothalamus. Forced wakefulness or diurnal sleep is a cortical and therefore a voluntary function. The cortex may either activate or inhibit the function of the hypothalamus. The reverse may also take place.

With regard to Dr. Goodhart's question about stupor, coma and other unconscious states, I believe that these states are phases of an exaggerated form of sleep disturbance and are regulated by the same centers and pathways. Frequently these terms are misused in clinical observations. The patient may be only lethargic and can be awakened if an attempt is made to do so; yet the record may describe him as in stupor or coma.

DR. C. P. OBERNDORF: I am not in a position to discuss the physiology of sleep because I am neither a physiologist nor an anatomist; so I shall confine my comments to our case. Perhaps I may begin by noting, in connection with Dr. Davison's comment on psychogenic factors, that there is no reason that a person with deep conflicts may not have encephalitis. The conflict would continue after, as well as before, the trauma to his central nervous system. Thus, a psychoanalyst reviewing such a patient's history would inevitably uncover these conflicts; the patient Dr. Davison reported on seems to have harbored every known tendency—from exhibitionism to incest. Therefore I do not think that his case is particularly cogent to the problem which we have presented, namely, the psychogenic factors in narcolepsy.

Dr. Brock asked why the patient did not manifest paralysis or some other symptom rather than narcolepsy as a result of her conflicts. It is not always easy to determine the nature of hysterical symptoms or the reason for the development of the particular symptom. To be sure, this patient did have a hemiparalysis. It was one of the signs which confused the diagnosis because her right hemiplegia may have been organic in origin. Perhaps complete paralysis would have meant death. Sleep, indeed, may have been a compromise symptom in preference to death, if one wishes to speculate why the somnolence developed as a symptom rather than a more serious or painful one.

One might emphasize that this patient had been ill with migraine headaches and nausea for twelve years before development of the narcolepsy. Why the narcolepsy began just when it did we cannot positively say, but after the death of the lover in the complicated situation (which we thought proper not to present here) she promptly went into her first and prolonged

sleep. It was a solacing evasion of and oblivion to a difficult situation.

Dr. Spiegel did most of the work on this case, but his material puzzled him. At that point he asked me to help, and I am grateful to him because the case aroused my interest, not so much from the fact that the narcolepsy seemed to represent an evasion but because the therapy produced such striking benefit. In refuting the idea of an organic lesion which resolved spontaneously, I must repeat that these symptoms had continued for nearly twelve years and the patient had been in the hospital for nearly six months, without improvement in her condition, before Dr. Spiegel began to treat her psychologically. One might maintain that whatever lesion was present in the ventricle disappeared at that time, but I question such an explanation. What interested me from the psychotherapeutic angle was the disappearance of a serious and long-standing condition on the basis of psychocatharsis alone.

I have been puzzled for many years as to whether the deep, penetrating and complicated analysis of unconscious mechanisms in psychoanalytic treatment may not at times complicate the patient's problems and settle him in a chronic preoccupation with his conflicts. Dr. Spiegel used a simple method in the treatment of a long-standing and severe illness—the original method of Freud—and the patient promptly began to get well. The thought occurred to me that this case was an outstanding example of the necessity for careful judgment in the choice of the application of psychoanalytic technic; I asked myself whether in certain cases such therapy does not prolong illness by too penetrating and too deep analysis. This is especially important today when the term "brief psychotherapy" is heard so often. What is meant by "brief" is still vague—whether it signifies that the patient is treated only over a short period, that the sessions are short or that the contact with the physician is superficial. Cases of this kind call attention to the need for discrimination in the employment of the method which Freud has made available and to the fact that many patients not only cannot, but should not, be treated by the deepest form of psychoanalysis.

Sequelae and Complications of Convulsive Shock Therapy. DR. B. L. PACELLA and DR. S. E. BARRERA.

The incidence of deaths occurring with the use of metrazol or electric shock therapy has been surprisingly low. Kolb and Vogel estimated a death rate of 1 per thousand among metrazol-treated patients and of 0.5 per thousand in electrical shock–treated material. Cardiovascular disturbances are usually mild, generally occur immediately after the seizure, with the patient exhibiting an irregular, slow pulse, and spontaneously clear up. In our own material hypertension developed in 2 patients subsequent to treatment, but more often lowering of the blood pressure occurred. Evidence of intracranial hemorrhage has not been observed. Pulmonary and respiratory complications are few, although postconvulsive apnea and stridor are commonly observed; these are readily overcome. The effect of treatment on healed or active tuberculosis is not yet clear, but patients with active tuberculous lesions have been treated successfully. Vertebral compression fractures occur in about 20 per cent of patients with whom hyperextension during treatment is employed, but symptoms are mild and disappear in a short time. Fracture of the long bones is extremely rare but may occur in elderly patients. Three patients in our series exhibited dizziness and 2 patients spontaneous convulsions after treatment. Electroencephalograms obtained prior to treatment from the latter 2 patients were abnormal. Histopathologic changes in the brain thus far reported have not been in substantial agreement with each other. Electroencephalographic changes produced by treatment have been largely reversible, although in a few instances they have persisted for periods exceeding six months. Memory defect resulting from treatment is a striking complication but generally disappears in a few weeks. It is concluded that the benefits derived from convulsion therapy in properly selected cases usually far outweigh the possible complications which may occur.

DISCUSSION

DR. S. BERNARD WORTIS: Dr. Pacella and Dr. Barrera are to be congratulated on the collection of data indicating that occasionally electric shock therapy can be given safely to the patient with mental disease who has an associated serious medical or surgical illness. Usually the physician will find it advisable to wait for his patient's medical condition to improve. Relative contraindications to shock therapy are severe hypertension, hyperthyroidism, tuberculosis, febrile conditions and active cardiovascular disease; I should be reluctant to advise electric shock treatment for a pregnant woman. The effect of this treatment on the fetus is not known. It is known that small hemorrhages occur as the result of severe convulsive movements, and it may be that such hemorrhages have a harmful effect on the fetus. However, occasionally the severity of the mental illness may warrant drastic treatment.

Since the motor convulsive phenomena are responsible for some of the complications, my associates and I at Bellevue Hospital have given a preconvulsive intravenous injection of sodium amytal. This diminishes the severity of the motor convulsive phenomena and lessens postconvulsive overactivity. For this purpose sodium amytal is safer than curare or betaerythroidine.

Almost every one has come to recognize that the treatment is disappointing for schizophrenia and the neuroses. One can see clinical improvement in patients with paranoid conditions after treatment, but generally the paranoid quality of the personality remains, even though the patient cannot focus on the particular subject that seemed to disturb him before therapy.

DR. HUBERT S. HOWE: Certainly, it is through a study of the dangers and complications of this treatment that one will learn how to overcome them. The dangers seem to be remarkably few in view of the violence of the procedure. The question of damage to the brain looms large in the minds of some investigators who have induced convulsive seizures in animals. Others have carried out similar experiments with no cerebral injury. In view of this disagreement, it is necessary for us as psychiatrists to follow the patients who have received this form of therapy and observe the results not only immediately, but months and years, after the treatment. We must ascertain whether their intellectual performance is on a level with their best normal activity. Comparison of electroencephalograms taken before, immediately and six months after completion of the treatment may also be of value. Such a careful followup study is being made at the New York State Psychiatric Institute.

Impairment of memory is the most obvious psychologic complication. This has never been serious or persistent in any of my patients, but from personal communications from other workers and from the literature there is little doubt that persistent incapacitating amnesia has been observed in some persons who have

received a large number of treatments with high voltages. In my experience, a course of from six to eight convulsive seizures is sufficient, and rarely have more than twelve been given during a short period, even in cases of schizophrenia. A few patients who were not completely relieved of depression have returned after a few weeks to have additional treatments. I believe that this is preferable to a longer course in the beginning.

At the Neuropsychatric Institute in Hartford, Conn., the Reiter apparatus is used, and not over 20 to 30 volts of current is employed. Patients treated by this method have no memory disturbance, but the application of the electrodes to the parietal regions and the vertex, instead of the frontotemporal areas, may also be a factor.

I wish to record a protest against administration of these treatments outside a hospital with a staff of trained assistants. Everything possible should be done to protect the patient from fractures, biting the tongue, headache, muscle pains and other minor complications which cause him to dislike and dread the procedure. I have a routine of preinduction medication which seems useful. Just prior to the treatment the patient is given 1 grain (65 mg.) of codeine phosphate and 3 grains (0.195 Gm.) of seconal sodium by mouth. . With this medication we have not had complaints of as severe headache and muscle pains as our patients had frequently experienced before this regimen was instituted. . The memory of after-confusion is less vivid and the whole experience less unpleasant.

I should like to ask Dr. Pacella what he thinks of the results of electric shock with the Reiter apparatus and whether he believes that this form of application will supersede the older method.

DR. LOTHAR B. KALINOWSKY: I can only agree with the practical conclusions of the authors, for I have worked with them in this field for years. I should like to comment on a few of the most disputed points.

One of the most frequent questions is whether organic changes are produced. My associates and I observed no microscopic changes in the brains of monkeys treated in the same way as our patients (Barrera, S. E.; Lewis, N. D. C.; Pacella, B. L., and Kalinowsky, L.: *Tr. Am. Neurol. A.* **68**:31, 1942). However, there is sufficient evidence that cerebral function is disturbed. Not only are electroencephalographic changes present, but the mental changes give evidence of organic changes. There are the memory defects; with them always go emotional disturbances, and in many patients more dramatic syndromes, even a delirium-like picture, appear. All the known varieties of symptomatic psychoses occurring with infectious-toxic diseases can be seen during a long course of electric shock treatments. But they are reversible, and even the most dramatic mental symptoms of organic origin usually disappear a week after the last treatment, except for slight impairment of memory, which may last longer.

A case which illustrates what Dr. Pacella has mentioned, that the relearning function is not seriously impaired, is that of a physician who was graduated abroad twenty years ago; he was deeply confused during the treatment of a depression and even lost his command of English. A few months later, however, he passed a state board examination.

I have treated several patients with tuberculosis; 2 of them were severely emaciated because they had refused food, and therefore the tuberculosis was aggravated by the mental condition. Both patients did well; one doubled her weight. I have also treated patients with schizophrenia complicated with traumatic epilepsy whose spontaneous convulsions did not increase, but disappeared during and several months after electric shock treatment, probably owing to the usual elevation of the convulsion threshold under convulsive treatment.

As to fatalities, I can only say that in my personal experience of almost 2,000 cases, I have not had a single death. A review of the literature reveals that several of the few fatalities were reported from hospitals where electric convulsive therapy is combined routinely with preconvulsion administration of curare. This indicates the risk of curare, which, therefore, I have not employed routinely, although its use is indispensable in certain cases. I have had no cases of fracture, since I avoid any tight restraint of the patient during the muscular discharge.

Administration of sodium amytal, as mentioned by Dr. Wortis, is recommended for two reasons: to prevent postconvulsive excitement (for this we use it in difficult cases, with excellent results) and to decrease the strength of the convulsion. The latter effect is obtained only with doses of 10 or 12 grains (0.65 or 0.78 Gm.). I have seen this decrease in the strength of the muscular discharge also with other anticonvulsive drugs, particularly with diphenylhydantoin, if these substances are given in amounts near the toxic level.

I wish to stress that, as Dr. Barrera and Dr. Pacella have shown, electric convulsive therapy is not invariably dangerous but has certain complications, and therefore should not be used when not definitely indicated. Its indiscriminate use should be warned against, particularly its constantly growing application in treatment of the neuroses, for many of which the extremely poor results do not justify the risks.

DR. B. L. PACELLA: The Reiter apparatus is an electric shock set, apparently of a new design, which is being used at the Hartford institute, and is still in an experimental phase. However, as Dr. Howe pointed out, it apparently produces substantially less memory defects than the forms in current use, and in some persons no memory disturbance can be detected clinically, even in the patient who had received, according to Dr. Howe, as many as twenty convulsive treatments. Not only does this apparatus employ a lower voltage, but the character of the electrical pulsations, that is the wave form, is somewhat different from that with other machines. The convulsion produced in the patient is essentially the same as that obtained with our present apparatus. The clinical impression of the physicians using it, who have also employed other electric shock sets, is that the therapeutic effects are about the same with all types of machines. There are certain disadvantages which I shall not discuss at present.

The important feature of this new apparatus is the apparently much less pronounced effect on the memory than is noted with use of the other sets. This may be disturbing to investigators who maintain that improvement or recovery depends largely on the disturbance in memory produced by the shock treatment. Another important feature noted in patients treated with the Reiter apparatus is that few electroencephalographic abnormalities are produced, even though a considerable number of convulsions is induced. Dr. Abraham Lieberson, who has carried on electroencephalographic studies on such patients, has shown me tracings obtained from patients who have had a large number of convulsions, in which only slight changes were found, an observation distinctly in contrast to the effect on the brain potentials with use of the present standard electric shock machines, in which the ordinary 60 cycle alternating current is utilized as the shocking stimulus. This observation is difficult to explain.

ILLINOIS PSYCHIATRIC SOCIETY

CLARENCE A. NEYMANN, M.D., *President, in the Chair*
Regular Meeting, March 2, 1944

Cerebral Malaria: An Electroencephalographic Study. DR. MANDEL SHERMAN, Chicago, and MAJOR W. PARK RICHARDSON, Medical Corps, United States Army.

The electroencephalographic investigation was made on soldiers with malaria who were hospitalized primarily for psychiatric observation and diagnosis. These patients presented the following symptoms: nausea and other gastrointestinal disturbances, weakness, headaches and dizziness and varying degrees of depression and lack of interest in their surroundings. Sixty-one patients with these symptoms who had malaria were compared with 30 patients with similar symptoms who did not have malaria. Definite abnormalities were observed in the electroencephalograms of 15 of the 61 malarial patients. This high incidence of abnormalities indicative of cerebral involvement is probably due to the fact that these patients represented selected cases from the malarial population, and not the frequency of cerebral disturbance in the general population.

The electroencephalographic changes included (1) abnormal waves of the delta type, with a frequency of 5 to 9 per second; (2) arrhythmia, which varied in degree from one patient to another, and (3) unusual changes in amplitude, indicating metabolic or other variabilities in the brain.

No change occurred with hyperventilation, such as is noted in patients with epilepsy.

A possible cause of electroencephalographic abnormalities associated with malaria is occlusion of the cerebral capillaries by the malarial bodies. Such an occurrence is not infrequent with malaria and has been pointed out by a number of pathologists. The fact that a high incidence was obtained for these patients although they were selected on the basis of their psychoneurotic symptoms indicates that a large number of cases of cerebral malaria may exist without recognition by the usual clinical methods.

DISCUSSION

DR. M. T. KOENIG, Chicago: How do these changes in the electroencephalogram compare with the records for other infectious diseases, such as typhoid, pneumonia and other conditions accompanied by symptoms of cerebral involvement?

DR. MANDEL SHERMAN, Chicago: The question is a bit too ambitious for present knowledge. From a survey of the literature I know that changes are associated with some of the conditions and that they are not similar to the abnormalities under discussion. With the usual toxic disorders there are no distinct electroencephalographic changes. The difficulty, of course, is to make an electroencephalographic study on a toxic patient. It is not usually done; but when an electroencephalogram is obtained, there are indications of "tension" rather than of the pathologic process seen in the records of the malarial patients.

DR. CHESTER DARROW, Chicago: The authors raised the question of the probable origin of the abnormal waves. The cause suggested, and one which must be considered seriously, is the occlusion of the smaller vessels by the parasites, with focal ischemia giving rise to an abnormal electroencephalogram. However, the authors rightly question the correctness of this interpretation since, if it were the explanation, there should be indications of a focal pathologic process. That such a focus was indicated by the electroencephalographic evidence is obvious from the essential similarity and synchrony of the larger slow waves in the two sets of records. In the record which was presented as more nearly normal there was even greater discrepancy between the two areas. It is questionable whether these effects truly arise from the cortex or represent a generalized cortical disturbance with, possibly, a deeper origin. My associates and I at the Institute for Juvenile Research have been interested in a problem related to the one presented here, namely, the electroencephalographic effects of encephalitis. Mr. Julian Pathman has been making a collection of records in cases of this disease, and there is a striking general similarity between the records he obtains and the records presented here. As the authors suggested, there is also the possibility of generalized damage, possibly arising from anemia or some other pathologic condition affecting the cerebrum as a whole, as well, perhaps, as deeper-lying structures.

I had hoped the authors might present the effects obtained at different stages of the malarial cycle. If one could have electroencephalographic records during the phase of actual fever, as well as before and after it, one might have a clue to the effects on cerebral activity of the actual disease process in the brain, as contrasted with possible residual effects.

Notwithstanding that abnormal results are obtained in a limited percentage of cases, it appears that a new field may be opened for the application of electroencephalography.

Homosexuality, Transvestitism and Psychosis: Study of a Patient Treated with Electric Shock. DR. SAMUEL LIEBMAN, Chicago.

The relation of homosexuality and transvestitism to psychosis has interested many psychiatrists. I had the good fortune to study a patient at the Norwich State Hospital (Conn.) who presented all these conditions.

The patient had been adopted at about 1 year of age by a maladjusted family. In this peculiar environment he early showed feminine interests. As he grew older, his interests became less masculine, until he became overtly homosexual, transvestitic and psychotic. The anamnesis revealed that 2 male siblings were homosexual and that the maternal side of the family had been heavily tainted for at least two generations.

After the administration of electric shock therapy the patient recovered from his psychosis and gave up his transvestitism. He was kept under observation for almost a year. Psychologic studies were made at intervals throughout the period of hospitalization and the subsequent period of observation. The changes in the patient's symptoms, ideation and mood under the conditions of hospitalization and follow-up study were interesting.

DISCUSSION

DR. D. B. ROTMAN, Chicago: The patients with transvestitism I have seen have been without psychosis; it seems to me that the conflicts in the present case of transvestitism precipitated the mental condition and that the cure effected by electric shock therapy was of schizophrenia, not of transvestitism. The more interesting cases of transvestitism I have seen have concerned persons who were not effeminate at all. I have particularly in mind a patient whom I had under treatment for six months. He was referred to me because

his expense account had gone so high that his father could not keep him in college any longer. He was using all his school money to buy feminine apparel from a fashionable dressmaker. This he wore secretly in his room before the mirror. But he had none of the attributes of effeminacy described in Dr. Liebman's case. At one time in his career he was so intent on appearing as a female that he insisted on undergoing an operation which would make him really look like a female when he put on the clothes he wished to wear in secret. He was able to finish a college course, that is, a period of four or five years, without detection of this impulse by his intimates.

Another point of interest to me in Dr. Liebman's paper is the fact that this person was a female impersonator. In court my colleagues and I see persons of this type in large numbers. Transvestitism is especially common among so-called male prostitutes. But I have never seen such a person thrown into a psychotic state by conflicts over his condition. Given a patient of intelligence, who is a transvestite and is not psychotic, is one, with present knowledge, justified in applying shock therapy? Has any one the courage to apply this form of treatment to such a condition? I feel that one of the finest research problems which could be undertaken in this community would be the hospitalization of a group of so-called sexual psychopaths with no abnormalities of the endocrine glands for a trial of shock therapy. I do not regard the shock treatment in the author's case, which was for schizophrenia, as at all related to such a problem.

DR. M. T. KOENIG, Chicago: Dr. Rotman's comments are interesting. The case struck me somewhat differently. If one will disregard the transvestitism for the present and consider this patient as he arrived at the hospital, overdressed, overdecorated and at the same time wearing men's clothes, and will follow the course of his psychosis and note his grandiose ideas, one will have the impression of a manic-depressive psychosis, of which the transvestitism was only a manifestation. The further progress of the condition seems to confirm this diagnosis. The irritability and paranoid trends are often observed in patients with manic states toward the time of recovery. Then with electric shock treatment the manic patient duly passes through his depressed state.

DR. VICTOR E. GONDA, Chicago: I know of a case exactly like the one Dr. Liebman presented. A well to do family adopted a child from the Evanston Cradle. At the age of 15 he was observed dressed in girl's attire and masturbating openly. The two policemen who found him took him home to his foster parents. Since the condition was serious, at least on the borderline of a psychosis, my colleagues and I undertook to treat the boy with electric shock, I am sorry to say, without result. It may be that we did not give him enough treatments.

As far as I know, transvestitism has not been treated successfully anywhere; it would be nice to start something new in Chicago.

DR. SAMUEL LIEBMAN, Chicago: I avoided making a diagnosis, for I did not want to commit myself. The only reference in the available literature in relation to the shock therapy of this personality disorder was that of Owensby, who treated 6 homosexual patients with metrazol. He claimed good results but did not follow his patients for any length of time. They were primarily transients, and I doubt the validity of the results.

The case I reported was worked up to prove to the other members of the staff at the Norwich State Hospital that environmental and psychologic factors are important in the development of personality disorders. The investigation brought out the profuse records of the other members of the family, but that is not a problem to be dscussed now.

The Conditioned Aversion Treatment of Chronic Alcoholism: Preliminary Report. DR. J. V. EDLIN, DR. R. H. JOHNSON, DR. PAUL HLETKO and DR. GERT HEILBRUNN, Chicago.

Owing to its known gravity and prevalence, the syndrome of chronic alcoholism does not invite an aphoristic restatement. Methods of treatment have in general pursued two goals: (1) the management of the withdrawal period and the immediate restoration of the patient's well-being, and (2) the inculcation of permanent sobriety, by utilization of individual or group psychotherapy, occupational and recreational activities and pharmacologic mediums. The achievement of the first goal is usually attained—the actual problem, however, arises after the acute withdrawal symptoms have subsided.

Reliable means of therapy were continually sought, and the new approach through establishment of an aversion to alcoholic beverages was deemed worthy of a thorough trial. The treatment consists essentially in establishing a reflex aversion to the sight, smell and taste of alcoholic beverages by means of an emetic. Eighty-five patients, with an average age of 38 and an average period of addiction to alcohol of twelve and one-half years, were treated. Of this total of 85 patients, 7 were treated outside the hospital as private patients. Four patients, or 58 per cent of this private group of 7 persons, have abstained from alcohol from three to seven months; 2 patients have relapsed, and reliable information on the fourth patient is unavailable.

A statistical evaluation of the results obtained with the entire hospital group cannot reflect the true merit of the treatment, and it is more advantageous to consider only the hospital patients who completed treatment at least five months ago. Sixty-four patients were treated between April and September 1943. Fifteen patients, or 23 per cent, are known to have remained abstinent for five to ten months. Follow-up information is unavailable on 22 patients, and 27 patients are known to have relapsed. This figure of 23 per cent is in contrast to the 58 per cent of favorable results obtained with the small group of patients privately treated.

The principal source of discrepancy in the results presented itself in the patient's sociologic situation as the probable reflection of his emotional and psychologic status. A survey of the records of the hospital patients disclosed a rather inferior social and financial situation, whereas all patients of the privately treated group and 11 of the 15 patients who were successfully treated at the hospital had a superior sociologic rating.

We concur in the consensus that every alcoholic patient suffers basically from a personality disorder and that the alcoholic debauch represents an escape from conflict. It is realized that the aversion treatment does not represent a "cure" at all—it must be regarded merely as a method to render the addictee abstinent for a certain period, during which psychotherapy, whether of the group form, such as attendance at meetings of the Alcoholics Anonymous, or individual, can be instituted and gain ground.

DISCUSSION

DR. JULES MASSERMAN, Chicago: This work by Dr. Edlin and his associates is to be highly commended on a number of counts: a well defined problem, a consistent technic, adequate follow-up studies and, best of all, an analytic and critical evaluation of results in the light of relevant and important psychologic and social factors. Moreover, the authors reach conclusions that are quite in accord with the modern psychodynamic concepts of alcoholism and its therapy—and it is perhaps only in this connection that I was assigned to supplement their discussion.

First, the authors correctly use the theoretic term "conditioning," not in the jejune pavlovian sense of mechanical reflexology, but, rather, to represent a process of adaptation in which meaning and motivation play essential dynamic roles. Meaning is never independent of the subject's conscious or unconscious interpretations of the situation; for this reason, a patient detained in a hospital and made to vomit an ipecac cocktail in a doctor's laboratory will obviously resolve never again to drink—that is, never again to drink an ipecac cocktail in a doctor's laboratory. But this resolution will not necessarily prevent him from imbibing good Scotch with a sympathetic friend at the nearest bar when he is sufficiently in need of the effects of alcohol and is free to obtain it on his own terms. As to motivation, Dr. Edlin and his coauthors showed that patients who after therapy again experience the need to escape from pressing economic and social problems are apt to resume their alcoholic intake under the stress of anxiety-ridden living. The final question as to the adaptative choice of the drug then arises: Why does a neurotic person take to alcohol? By what pharmacologic magic does alcohol fill the needs of a neurotic person so specifically that he will seek it avidly to the point of intractable addiction? Rado, Knight, Schilder and others pointed out the oral, homosexual and other symbolic unconscious satisfactions that alcoholism facilitates, but their valuable psychoanalytic studies still did not explain the special needs for the drug itself rather than for other forms of oral indulgence, or the corresponding addiction of patients with similar neurotic mechanisms to sedatives, hypnotics and opiates not necessarily taken by mouth or in homosexual camaraderie. However, recent experimental studies in my laboratory may furnish a remote clue to this problem. Briefly, it was observed that when alcohol was administered to normal animals, they were no longer sensitive to the complex demands of their environment and reverted to more simple, directly satisfying, though somewhat disorganized, activities. When an experimental neurosis was induced in these animals by subjecting them to a severe motivational conflict, alcohol was again successful in abolishing complex "neurotic" adaptations, such as inhibitions, phobias and compulsions, and in this way the drug appeared to give the animal demonstrable relief. Moreover, some of the animals soon associated the drug with these effects and began to prefer foods that contained alcohol to foods that did not. In other words, the animals became alcohol "addicts" and remained so until the neurosis was relieved by some form of therapy and the need for the effects of alcohol thus abolished. If the qualifications necessary in evaluating such animal experiments are neglected for the moment, one fact emerges: A neurosis is a psychobiologic tension state that is symptomatically relieved by alcohol. When this is translated, however broadly, into operational terms, one may confirm experimentally the clinical observation of Edlin and his co-workers, and nearly all others in the field, namely, that an alcoholic addict will continue to seek and imbibe his drug as long as his neurotic needs for its pharmacologic and psychologic effects continue. The treatment of alcoholism, then, must be more than merely symptomatic: In the last analysis, the underlying neurosis must be attacked by every medical, psychologic, economic and social means at one's command. Obviously, the authors of the paper have reached the same implicit conclusions.

DR. CHESTER DARROW, Chicago: Were the patients informed that there was ipecac in the drink?

DR. FRANZ ALEXANDER, Chicago: The two papers presented here in which the shock therapy for psychosis and the treatment of alcoholism were considered have one feature in common—they represent something which might be called symptomatic therapy, an approach which the rest of medicine tries to replace more and more with the etiologic attack. This is not meant as a criticism; it is merely a statement of fact. Dr. Masserman's films forcefully demonstrated that alcoholism is a symptom, not a disease. Only neurotic cats prefer alcohol, for it relieves them of certain conflicts. The conflict is the cause and alcoholism the resulting symptom.

I must, however, defend Dr. Rado from Dr. Masserman's criticism, because in his paper on drug addiction he came to similar conclusions, namely, that alcohol, through its narcotic effect, relieves basic conflicts and thus creates the craving for alcohol. This is also true of morphine and opium. The main issue is that alcohol, by its narcotic effect on the higher centers, temporarily removes inhibitions and thus relieves the complex conflicts of emotional life. Probably something similar takes place in shock treatment, except that its influence on the higher centers lasts somewhat longer. I wish to emphasize that both conditions discussed tonight, alcoholism and schizophrenia, are chronic disturbances of long duration. In my experience of twenty-two years, I have learned to look on both the psychotic and the alcoholic patient from a long range point of view. I cannot see the validity of speaking of a cure of such a condition when the result lasts only about nine months. What is nine months in the life of an alcoholic addict? I should speak of the symptom-free periods as remissions. Remissions of six to nine months are common with alcoholic patients, who from time to time "go on the wagon."

The psychotic patient whose case was described here was treated with shock; he had a relapse and was given shock therapy again; the chief result was the change in form of his symptoms. For a while he was even free from symptoms. However, in the case of the patient with a psychosis, combined with transvestitism, a remission of nine months or a year does not mean much. The underlying condition is still there; otherwise why should he relapse again and again? And if such a patient does not relapse, I should require a thorough investigation of the situation in order to decide whether the remission is not due to changed conditions. In this type of therapeutic research I should like to see it taken for granted that alcoholsm or the manifestations of schizophrenia are symptoms, and not the basic condition. In internal medicine one is not much impressed when the patient's headache is relieved by administration of acetylsalicylic acid and the basic condition is left unchanged. Psychiatrists are not yet clearly aware of the difference between the symptomatic approach and the etiologic attack on the basic condition, and they continue to forget that the symptoms are nothing but the self-curative attempts of the organism.

Dr. Edlin and his associates were aware of the symptomatic nature of their treatment, but I should have liked even more emphasis on this part. Dr. Liebman's patient exhibited schizophrenia, transvestitism, homosexualism and, finally, criminal behavior. I wonder what he will show after a new series of shock treatments?

DR. CONRAD S. SOMMER, Chicago: I discussed this subject with the authors before they began their study and had an agreement with them that certain criteria should be followed in the selection of cases. However, I presume that in order to get enough cases to serve as a basis for the completion of the paper some of these criteria were disregarded. Since, however, the criteria apply to the selection of cases with regard to the social and vocational adjustment, I should like to indicate them briefly: 1. The patient should be in sound physical condition, and the alcoholism should not be accompanied by psychosis. 2. The patient should show interest in therapy and voluntarily apply for it. 3. There should be evidence of family support and interest in the treatment, as demonstrated by a relative or a close friend. 4. The patient or the family should supply the necessary alcoholic beverages as further evidence of his or their interest and as an indication of cooperation in follow-up studies. 5. The conditioned reflex treatment is successful only as already mentioned, in producing a temporary aversion to drinking. The conditioned reflex treatment will not make a new man out of one who has never made a successful adjustment in the first place. But it conceivably can, and, it is to be hoped, will give an alcoholic person enough of a breathing spell from his alcoholism so that his will to stop drinking has a chance to assert itself. Hence, a futher requirement for admission to the conditioned reflex treatment is that the patient shall have had at least three years of successful work experience.

I suggest that the authors reevaluate their successes and failures in the light of their observance of these criteria.

DR. GERT HEILBRUNN, Chicago: The discussions need no further comment; it is sufficient to stress again that the conditioned aversion treatment cannot be considered a cure for alcoholism. However, in a considerable number of cases it establishes a period of abstinence which may and should be utilized for a psychotherapeutic approach. My colleagues and I agree with Dr. Alexander in his observation that alcoholic patients may have spontaneous periods of abstinence lasting from six to nine months. The overwhelming majority of our patients, however, had indulged in the use of alcohol continuously, so that there was no opportunity for a psychotherapeutic approach to gain ground.

In response to Dr. Darrow's question, the patient is informed before the start of the therapy that he will receive a medicament mixed in his first drink to educe the obnoxious qualities of the alcohol.

CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *President, in the Chair*
Regular Meeting, March 14, 1944

Herniation of Cervical Intervertebral Disks. DR. PAUL C. BUCY and DR. HARVEY CHENAULT.

Two cases of herniated cervical intervertebral disk were reported, with compression of the seventh cervical nerve root in 1 and of the sixth cervical nerve root in the other.

In the first case, that of a man aged 41, herniation of the intervertebral disk between the sixth and the seventh cervical vertebra, with compression of the right seventh cervical root, occurred as the result of a fall on an icy street. This condition gave rise to repeated attacks of severe pain just below the medial part of the spine of the right scapula and to persistent paresthesias of the thumb and the index and middle fingers and the radial border of the forearm, all on the right side. Removal of a small piece of herniated cartilaginous material through a partial hemilaminectomy opening gave immediate and complete relief from all symptoms.

In the second case, that of a women aged 31, an automobile accident caused herniation of the intervertebral disk between the fifth and the sixth cervical vertebra, causing compression of the left sixth cervical nerve root. She experienced immediate pain at the base of the neck on the left side. A few days later this pain began to radiate across the shoulder, down the outer aspect of the arm and out to the end of the thumb. It was usually a constant dull ache, but moving the arm or the neck often evoked a sudden, sharp burst of pain which radiated from the neck down the arm and into the thumb.

Roentgenographic examination disclosed loss of the normal curvature of the cervical portion of the spine, reduction in the intervertebral space between the fifth and the sixth cervical vertebra and slight hypertrophic bony changes at this joint.

These 2 cases emphasize that the sensory area supplied by the sixth cervical root centers about the thumb, while the sensory distribution of the seventh cervical root is concerned primarily with the index finger.

DISCUSSION

DR. FREDERICK HILLER: On what clinical evidence do the authors make the differential diagnosis of herniated disk and secondary narrowing of the neural foramens?

DR. ADRIEN VERBRUGGHEN: I have reported 4 cases of this condition before this society (Prolapsed Cervical Intervertebral Disks, ARCH. NEUROL. & PSYCHIAT. **52**:251 [Sept.] 1944) in which the typical signs were not presented. In 2 cases the index finger was the only one involved, but in 2 other cases, in which the sixth and seventh roots were compressed, there was no anesthesia or any other neurologic sign except in the roentgenogram. As a matter of fact, this afternoon my associates and I operated in another case in which there was a narrow disk between the fifth and the sixth cervical vertebra, with no objective neurologic signs, but with great pain. I should like to ask Dr. Bucy whether he has any explanation for the fact that the postaxial elements of the root are more involved than the preaxial elements in the sciatic and in the cervical syndrome. I have asked many people, but so far I have not had a good answer. I have no answer myself.

DR. PAUL C. BUCY: I can conceive of there sometimes being great difficulty in differentiation from arthritis with compression of the root either by thickening of the soft tissue or by bony proliferation at the intervertebral foramen. In most cases the differentiation will rest on several factors. One is the localized nature of the pain. Usually a patient with a herniated disk is insistent on the localization of his discomfort, whereas the patient with arthritis of the spine has more diffuse discomfort, which is often bilateral and involves more than one root. With arthritis the discomfort is often

more gradual in its development than that with herniated disk. The roentgenogram is helpful in some cases, although it is conceivable that a patient may have both arthritis and a herniated disk.

It is possible to have a herniated vertebral disk and a normal roentgenogram, as occurred in the first of the 2 cases reported. The roentgenographic signs when present are not striking. They are limited to one intervertebral space. That space is reduced in width as compared with all the other spaces; the normal curvature of the cervical part of the spine is lost at the point of the herniation, and there may be proliferative bony changes, which are limited to that level.

Paralysis of Nerve Induced by Direct Pressure and by Tourniquet. DR. DEREK DENNY-BROWN and DR. CHARLES BRENNER.

This paper was published in the January 1944 issue of the ARCHIVES, page 1.

DISCUSSION

DR. PAUL WEISS: I am somewhat embarrassed to be called on for comment, for I should prefer not to have to contradict the distinguished visitor.

I have been working on experimental nerve compression for two years and, with my collaborators, have studied well over 100 cases. We have observed and described the following effects: (1) pressure block of conduction; (2) preservation of axis-cylinders in the compressed zone; (3) edema proximal to the constriction; (4) damming of the axoplasm proximal to the constriction, and (5) swelling of degenerated fibers distal to the constriction.

Dr. Denny-Brown's pictures furnish beautiful confirmations of our observations. They also add a new point in understanding of the fate of myelin under compression. I must disagree, however, with the interpretation given by Dr. Denny-Brown that these phenomena are due to interference with the blood supply rather than to a direct disturbance of the nerve fibers. My colleagues and I have presented seemingly conclusive experimental evidence that constriction affects the nerve fibers directly. Some of the evidence may be briefly restated.

Pressure Block.—In joint experiments with Dr. Hallowell Davis, excised peripheral rat nerves were provided with fitting cuffs of living artery and stimulated at one end, and oscillographic records were taken from the other end. When the arterial cuffs were made to contract by application of epinephrine, conduction of impulses was blocked within a few minutes. On redistention of the vascular cuffs conduction returned. That the block was due to the mechanical disturbance, and not to ischemia and anoxia, is plain not only from the fact that blood supply to the nerve was absent and access of oxygen to the surface of the nerve was as much restricted in the unconstricted as in the constricted cuffs, but from the promptness with which the block developed.

Dr. Denny-Brown has referred to Grundfest's observation that nerve conduction is abolished only by very high pressures. In this he overlooks the fact that in Grundfest's experiments the whole nerve was enclosed in a medium which was placed under even pressure, so that the fibers could remain intact, whereas local constrictions always produce displacement of neuroplasm. Obviously, conduction is blocked by this local disorganization of the axon, rather than by pressure as such. Grundfest's results are therefore of no relevance to the problem of nerve constriction. Moreover, Dr. Denny-Brown has emphasized that tourniquet block often affects the motor fibers alone, to the exclusion of the sensory fibers. Can sensory fibers subsist in anoxia? If not, anoxemia cannot have been severe enough to account for the motor block.

Preservation of Compressed Axis-Cylinders.—The fact that axons in a constricted zone fail to undergo wallerian degeneration, as observed by Ramón y Cajal, Stroebe and us, is beautifully illustrated by Dr. Denny-Brown's slides. But, again, this effect cannot be laid to ischemia because it can likewise be obtained in vitro. My colleagues and I have shown that in excised nerves placed in isotonic solution of three chlorides U. S. P. and subjected to partial constriction wallerian degeneration is inhibited throughout the constricted portion, whereas the mere covering of the surface without constriction had no effect. Therefore, constriction interferes with fiber degeneration directly, and not by way of ischemia.

Edema.—Dr. Denny-Brown describes swelling of the nerve on both sides of a constriction. My associates and I have previously described the same phenomenon. However, we have insisted that the nature and origin of the swellings are altogether different on the central and on the peripheral side: Centrally there is accumulation of interstitial liquid between the nerve fibers, while distally the individual fibers become vacuolated and swell but remain closely packed. In line with common terminology, we designate only the former swelling as edema. Dr. Denny-Brown prefers to call both conditions edema. I am glad to note that the difference of opinion between him and me in this matter has arisen merely from his use of the same term for two different phenomena. The interstitial edema is proximal. This position indicates that it is not primarily of vascular origin. My associates and I have concluded that it results from the damming up of endoneurial fluid in centrifugal motion. We have recently confirmed the existence of this endoneurial flow by radioactive tracers. At any rate, the proximal interstitial edema must not be confounded with the traumatic swelling of the distal fibers.

The preceding critical comments bear on matters of evidence and interpretation. They should not be allowed to overshadow my admiration for the excellence of Dr. Denny-Brown's observations and illustrations. Furthermore, if I advocate the view that constriction acts on nerve and nerve fibers directly, I am referring to the primary effects only. There is no doubt that ischemia will likewise leave its mark on the nerve through secondary effects. However, to distinguish the direct from the indirect effects must remain a matter of future analysis, rather than one of mere assertion.

DR. FREDERICK HILLER: I have been fascinated by this paper, as would be any one who has studied the problem which Dr. Denny-Brown has discussed. My associates and I have carried out experiments concerned, among other problems, with the effect of nerve traumatization as encountered particularly in gunshot wounds. The results of these studies are soon to be published. I can confirm Dr. Denny-Brown's observations. Nerve contusions produced by a bullet that has passed through the thigh of a cat, more or less close to the sciatic nerve, afford a particularly good opportunity to study the effect of trauma on the nerve. We observed that the traumatization varied in degree in the different fasciculi. Cats were allowed to survive the trauma from several days to many weeks, and we observed the nature of the traumatic effect in its degenerative and regenerative phases. The traumatized nerve shows not only the well known wallerian degeneration but areas of

necrosis, the latter differing histologically from the former. It is surprising that these necrobiotic phenomena should have escaped the notice of practically every one who has worked on the problem of nerve damage and nerve regeneration. They can be seen not only in traumatized portions of a nerve but in grafts in which lack of circulation leads to a breakdown of the ectodermal elements. The necrobiotic destruction of the myelin fails to show the characteristic phases of the wallerian degeneration, namely, the typical dark-stained myelin globules and the large fat droplets. The necrotic decomposition products fill not only the endoneural tubes but, as Dr. Weiss mentioned, the intertubular spaces as well. Edema is seen frequently. I agree with Dr. Denny-Brown that an ischemic lesion is the probable explanation of this sort of tissue reaction. The necrobiotic process apparently has a stimulative effect on the endoneural cells. A strong mesodermal proliferation takes place in traumatized nerve fasciculi, leading to more or less profound obliteration of the original structure of the endoneural tube. Proliferation of Schwann cells and regeneration of nerve fibers follow the proliferation of the mesodermal endoneurium, and the arrangement of the regenerated nerve fibers becomes just as irregular and confusing as that of the mesodermal cells and fibers. The isomorphous structure of a normal nerve, retained in the neurotization of a nerve in secondary degeneration, becomes heteromorphous in traumatized portions of a nerve, as well as in most nerve grafts. Traumatized myelin may also form a lasting barrier to the outgrowth of axons, leading to the formation of Perroncito spirals. The general belief that these spirals are the effect of connective scar tissue, with obstruction of nerve regeneration, is certainly wrong.

DR. DEREK DENNY-BROWN: I am grateful to the discussers for bringing out so many interesting points. Dr. Weiss differs from me in some respects, partly with regard to the length of nerve compressed and partly with regard to his in vitro technic. The preservation of myelin tubes with loss of nuclear staining in the zone of severe compression, and with degeneration on either side of that zone, seems to me to warrant use of the term "preservation necrosis." It is not clear to me that nerve compressed between cover slips in vitro should be as well oxygenated at its center as at its periphery, and I suspect therefore that factors other than pressure, delay wallerian degeneration, but I am not familiar with the technic.

The difference between Dr. Weiss's view of edema and mine is derived mainly from a difference in opinion as to the nature of the swelling of a nerve distal to a compressed zone. The nerve fibers are more swollen distally; I agree that there may be less endoneural fluid in proportion, but would point out that the nerve fibers are then in degeneration and are themselves edematous. I prefer therefore to regard both the proximal and the distal swellings as edema.

I am not wholly satisfied that vascular stasis is the whole explanation of edema, for if it were the histiocytic infiltration and the endoneural proliferation would still have to be accounted for. I was greatly interested in Dr. Hiller's description of the early loss of myelin and of preservation of Schwann sheaths in nerves contused by a bullet. I have a suspicion, derived from experiments on percussion of nerves, that fragmentation of myelin is the primary cause of the histiocyte response. The endoneural reaction remains for months after the cause of compression is removed and may be the only residual sign of a compression lesion. The mechanism of the endoneural response is tied up with the whole problem of the cause of neuroma.

Injuries of the Vertex of the Skull with Special Reference to the Paracentral Lobules of the Brain. DR. JOHN R. GREEN and DR. ERIC OLDBERG.

Two cases of bilateral injury to the paracentral lobules of the human brain are presented. The influence of such lesions on sphincter control is reviewed and discussed. The superficial clinical similarity between symptoms and signs of injuries to the spinal cord and corresponding indications of lesions of the paracentral lobules is pointed out, and suggestions with regard to the differential diagnosis are made.

This paper was published in full in a previous issue of *Surgery, Gynecology and Obstetrics* (**79**:267 [Sept.] 1944).

DISCUSSION

DR. DEREK DENNY-BROWN: Bilateral lesions of the paracentral lobules must be rare. I remember 2 cases of such lesions, in each of which loss of pain and touch was present in the lower extremities, as described by Foerster, a symptom making their resemblance to cases of lesions of the cord even more complete. I have no explanation for this phenomenon.

Micturition is a roundabout and indirect voluntary act, comparable to salivation. It would seem that the inhibition of an inhibition would best explain the course of events. There is no convincing evidence that the process can be initiated from any region of the motor cortex. Yet there is no doubt that lesions of the parietal area can interfere with the function, making voluntary micturition difficult or impossible. Bilateral lesions of the frontal area, on the other hand, facilitate the process and lead to incontinence. In the cases I recall, the bilateral lesions of the parietal area had also caused loss of position sense and hypotonia in the lower limbs, and the dysuria then appeared to be correlated with the underactivity of reflexes shown by the hypotonia. In the cases presented by Dr. Green and Dr. Oldberg the condition was described as spastic, and this observation appears to set the depression of micturition aside from the general state of other reflexes. Perhaps the difference would have been less pronounced with longer survival.

Book Reviews

The Management of Neurosyphilis. By Bernhard Dattner, M.D., J.D., with the collaboration of Evan W. Thomas, M.D., and Gertrude Wexler, M.D. Foreword by Joseph Earle Moore, M.D. Price, $5.50. Pp. xiii, plus 398 and 27 tables. New York: Grune & Stratton, Inc., 1944.

Dattner's book comes at the beginning of a new era, the penicillin era, in the treatment of neurosyphilis. While this particular drug is still in its infancy, Dattner can look back on two decades or more during which the treatment of neurosyphilis has been revolutionized by the introduction of malaria and pentavalent arsenicals. He consequently gives a scholarly presentation of what has been accomplished between the two world wars in a battle against the disease with which he has been closely identified.

The author brings a freshness of view to the subject. Instead of dealing with the clinical symptomatology and differential diagnosis of neurosyphilis, he relies for both diagnosis and prognosis, and even for therapeutic control, on examination of the spinal fluid. Instead of describing the time-honored intravenous and intrathecal treatments, he jumps right into a discussion of malaria therapy, insisting that as soon as the diagnosis is made the patient should be inoculated. At the same time, however, he gives the historical background and development of various other methods of therapy, with fairly detailed discussion of the favorable and unfavorable results. The discussion is so detailed at times that the author is apt to submerge his own outstanding observations in the large amount of material collected from the literature.

This work is rather strictly a clinical survey, written for the physician who will treat neurosyphilis. Its emphasis on the minutiae of spinal puncture will strike the average physician as absurd in view of the fact that he has been doing spinal punctures since he was a medical student. The same may be said for the laboratory tests, for which the therapeutist relies on the clinical laboratory. A detailed consideration of these procedures does not have a place in a work of this type. More helpful would be a discussion of the relative values of the complement fixation and the flocculation tests and the variations in the colloidal reactions. A chapter on the pathology of the disorder and its response to therapy would also be welcome. Theoretic considerations are given their proper emphasis, and social aspects are handled in a paragraph that deserves to be quoted because of its idealism.

"Only a few words are necessary to refute the objections frequently raised that the modern therapeutic methods in general paresis [dementia paralytica] quite often prolong the life of a patient without enabling him to return to his former occupation and to resume his social functions. These patients put a burden on the community because they must be cared for in state institutions. It has been suggested that a preliminary selection of patients ought to be made, to exclude from the benefit of treatment those patients who offer little chance of social recovery. From a strictly medical point of view this suggestion does not even deserve discussion. How are we going to decide whose life should be saved and whose sacrificed? Who can determine in every case what the end results of therapy will be? It is the duty of the medical profession not to waste time with fruitless attempts at treating late neurosyphilitic patients by methods that time and again have proved ineffective, and not to wait until clinical symptoms manifest themselves even to the layman. We cannot be held responsible when the pathologic process can only be arrested on a low level, because the patient was delivered into our care too late. Furthermore, if new therapeutic methods are to be tried, they should be applied exclusively to those patients in whom procedures that are generally accepted as effective have failed, or to patients who are so far advanced that no therapy offers good prospects of recovery."

Dattner's collaborators deserve much credit for maintaining readability in this important work. The reviewer recalls some fatiguing hours spent in wrestling with the idiom of Dattner's previous (1933) work on the subject. The bibliography and index render the book a first rate secondary source for the researcher of the future who will be concerned with the malaria era of neurosyphilis.

News and Comment

AMERICAN NEUROSURGEONS INVITED TO THE FIRST SOUTH AMERICAN CONGRESS OF NEUROSURGEONS

The First South American Congress of Neurosurgery will be held at Montevideo, Uruguay, March 1 to 4, 1945. An invitation to attend the Congress has been officially extended to North American neurosurgeons by the president, Prof. Dr. Alejandro H. Schroeder. Prof. Agdo. Dr. Román Arana Iñignes, Montevideo, Convencion 1287, is General Secretary of the Congress.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASES

The Association for Research in Nervous and Mental Diseases, at its annual meeting held in New York on Dec. 16, 1944, voted to center its program for the meeting a year hence on the subject of epilepsy and convulsive disorders. Officers for the coming year are: president, Dr. William G. Lennox; vice presidents, Dr. H. Houston Merritt and Dr. Wilder Penfield, and secretary-treasurer, Dr. Thomas E. Bamford Jr.

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BLOOD SUPPLY OF THE NERVES OF THE UPPER LIMB IN MAN

SYDNEY SUNDERLAND

MELBOURNE, AUSTRALIA

Investigations on the blood supply of peripheral nerves by Quénu and Lejars[1] (1890, 1892), Bartholdy[2] (1897) and Tonkoff[3] (1898, 1907), toward the close of the last century, extended the rather limited observations previously made by Haller[4] (1756), Isenflamm and Doerffler[5] (1768), Bichat[6] (1830) and Hyrtl[7] (1859, 1864) and culminated in the publication of a series of papers which made available a considerable body of accurate information on this subject. It is perhaps unfortunate that these reports appeared at a time when interest in the peripheral nervous system was dominated by the problems of degeneration and regeneration and by the behavior of the apparently more active elements of the nerve in those processes, namely, the axis-cylinder and its myelin and Schwann sheaths. As a result, any possible effect of the blood supply on axonal conduction, degeneration and repair failed to attract attention, though suggestions that occlusion of the vasa nervorum might be responsible for certain disorders of peripheral nerve function did appear from time to time in the literature (Lapinsky,[8] 1899, and others). Thus, in 1907 Tonkoff[3b] was drawn to protest:

> . . . den Arterien der Nerven bis jetzt zu wenig Beachtung geschenkt worden ist; in den Lehr- und Handbüchern werden sie meist ganz übergangen oder doch nur oberflächlich erwähnt.

Even as late as the great war of 1914 to 1918, when extensive investigations were undertaken for the purpose of extending knowledge of nerve structure and nerve function as a basis for improvement in the diagnosis and treatment of the nerve injuries which had accumulated in such large numbers, the possibility that the vasa nervorum might be implicated failed to arouse much interest.

There are signs, however, that this defect is being remedied. In 1926 Ramage,[9] unaware of the contributions of Tonkoff and of Bartholdy, reexamined, in the light of the observations of Quénu and Lejars, the blood supply to the large peripheral nerves of the upper limb in man. The present world conflict has given a new impetus to the study of peripheral nerve injuries; physiologists are now appreciating the functional significance of the blood supply to nerves, while the consequences of pathologic changes in the vasa nervorum are not being neglected. The observations of Quénu and Lejars, Tonkoff, Bartholdy and Ramage on the anatomic features of the vasa nervorum, however, remain the most informative and accurate available.

Studies on peripheral nerve injuries at a military hospital in Australia have inevitably introduced problems requiring for their solution precise knowledge concerning neurovascular relationships. Reference to the relevant literature has shown that previous investigations failed to provide certain essential details relative to the arterial supply of individual nerves. Moreover, the material used in the earlier work was predominantly fetal in type, and this suggested that a more extensive investigation into the supply to individual nerves in a larger series of adult arms was desirable in order to determine whether postnatal changes in any way modify the extraneural and intraneural distribution of the vasa

From the Department of Anatomy and Histology, University of Melbourne.

1. Quénu, J., and Lejars, F.: (*a*) Les artères et les veines des nerfs, Compt. rend. Acad. d. sc. **111:** 608, 1890; (*b*) Étude anatomique sur les vaisseaux sanguins des nerfs, Arch. de neurol. **23:**1, 1892.

2. Bartholdy, K.: Die Arterien der Nerven, Morphol. Arb. **7:**393, 1897.

3. Tonkoff, V. N.: (*a*) Die Arterien der Intervertebralganglien und der Cerebrospinalnerven des Menschen, Internat. Monatschr. f. Anat. u. Physiol. **15:**353, 1898; (*b*) Die nervenbegleitenden Gefässnetze beim Embryo und die Arteriae nutriciae nervorum beim Erwachsenen, Anat. Anz. **30:**471, 1907.

4. Haller, A.: Icones anatomicae, Göttingen, A. Vandenhoeck, 1756.

5. Isenflamm, J. F., and Doerffler, J. F.: De vasis nervorum, Erlangen, 1768.

6. Bichat, M. F. X.: General Anatomy, London, 1830, vol. 1, p. 168.

7. Hyrtl, J.: (*a*) Oesterr. Ztschr. f. prakt. Heilk., 1859; cited by Tonkoff[3b]; (*b*) Denkschr. d. math.-nautrw. Cl. d. k. Akad. d. Wissensch., 1864, p. 23; cited by Tonkoff.[3b]

8. Lapinsky, M.: Ueber Veränderungen der Nerven bei acuter Störung der Blutzufuhr, Deutsche Ztschr. f. Nervenh. **15:**364, 1899; cited by Adams.[10]

9. Ramage, D.: The Blood Supply to the Peripheral Nerves of the Superior Extremity, J. Anat. **61:**198, 1927.

nervorum. It may be mentioned here that the results of the present study indicate that there are no postnatal changes of any significance in the vascular pattern. For the purpose of checking the observations of earlier investigators and of extending them wherever possible in terms of modern requirements, the normal distribution of the vasa nervorum has been reinvestigated in a larger series of adult arms than has hitherto been examined. It is not proposed in this report to review in any detail the literature on the subject. This has recently been covered in an excellent review by Adams [10] (1942), whose paper also contains a comprehensive bibliography.

MATERIAL AND METHODS

Observations were made on the blood supply of the median, ulnar and radial nerves in adult human arms by means of the following methods:

1. The extraneural features of the vasa nervorum to all three nerves were investigated by dissection in 37 adult arms. An examination of the pattern in both arms in 8 subjects permitted a comparison of the disposition of the vessels on the two sides; the remaining 21 arms were unpaired. In each nerve the blood supply was examined from the origin of the nerve in the axilla to the distal border of the flexor retinaculum.

2. The intraneural vascular pattern was studied macroscopically and microscopically.

(*a*) Macroscopic study: The pattern was outlined by intra-arterial injection of colored gelatin or india ink in limbs freshly amputated for conditions not affecting the blood vessels or nerves. After the injection the nerves were dissected, removed, dehydrated and cleared in cedar-wood oil. The intraneural pattern was then traced by direct observation and microdissection.

(*b*) Microscopic study: (1) After examination of the extraneural relations in the 37 specimens the nerves were removed and studied histologically. Ten segments, each 1 cm. in length, were cut from the median and the ulnar nerve. The first segment was taken in the axilla; the fifth, at the elbow, and the tenth, at the wrist. Of the remaining segments, the second, third and fourth were evenly spaced between the axilla and elbow, and the sixth, seventh, eighth and ninth, between the elbow and the wrist. In view of the large number of vessels usually reaching the ulnar nerve in the neighborhood of the medial epicondyle, this nerve was sectioned not only in the groove but immediately above and below it. In the case of the radial nerve, segments were taken from the axilla, at the entrance to the spiral groove, in the groove and in the muscular furrow between the brachioradialis and the brachialis muscle. The fifth, and last, section included the terminal portion of the nerve and the first parts of the posterior interosseous and superficial radial nerves.

Each segment was fixed in the usual manner and embedded in paraffin. The transverse sections, 15 microns in thickness, were cut from each block and stained with hematoxylin and eosin. This material gave valuable information concerning the size, type and disposition of the vessels in different nerves and at different levels of the same nerve.

(2) The intraneural pattern was also studied by examining transverse and longitudinal sections of fresh nerves, cut at 250 microns, in which the vessels had been outlined by Pickworth's sodium nitroprusside method.

(3) Additional information concerning the intraneural pattern was obtained from the examination of transverse and longitudinal sections, 250 microns in thickness, of the injected nerves.

10. Adams, W. E.: The Blood Supply of Nerves: 1. Historical Review, J. Anat. **76**:323, 1942.

NOMENCLATURE

In order to avoid any confusion concerning the terminology employed in describing the histologic features of the nerve and its contained vessels, it is proposed to outline briefly the nomenclature employed in this investigation.

The Vessels.—The structure, and not the size, of the vessel was used as the sole basis for classification. The lumen of a vessel can be modified so readily by physical and chemical agencies and is subject to so many variations during life that its size was disregarded.

A capillary is defined as a vessel in which endothelium is the sole component of the vessel wall. This endothelium is not folded.

A precapillary, or precapillary arteriole, is lined with a layer of unfolded endothelium, outside which is a simple, thin circular coat of smooth muscle, one to two cells in thickness.

An arteriole has a wall composed of three recognizable layers. The lumen is lined with endothelium, external to which is an internal elastic membrane. Owing to the presence of this elastic layer, the lumen is irregularly folded. The intermediate layer, or tunica media, is composed predominantly of smooth muscle. The most external layer, or tunica adventitia, is composed of fine fibroelastic tissue. It is thin and ill defined and merges without any sharp line of demarcation into the surrounding connective tissue. With the exception of the median artery, no vessels larger than arterioles have been seen in the sections of the nerves examined.

The postcapillary venules which drain the capillaries have in general thinner walls than the corresponding precapillary arterioles, while, in addition, the smooth muscle coat is absent. In the larger adjoining venules the wall is very thin in relation to the size of the lumen and is composed principally of connective tissue with a trace of smooth muscle. The large lumen, the very thin wall and the predominance of connective tissue in the wall are readily identifiable features.

The Nerve.—The intraneural disposition of the vessels is best expressed in terms of the internal architecture of the nerve. The nomenclature used is illustrated in figure 1 *A*. The individual nerve fibers are collected into fasciculi, oval or circular on transverse section, each of which is surrounded by a ring of dense white fibrous connective tissue. This is the perineurium,

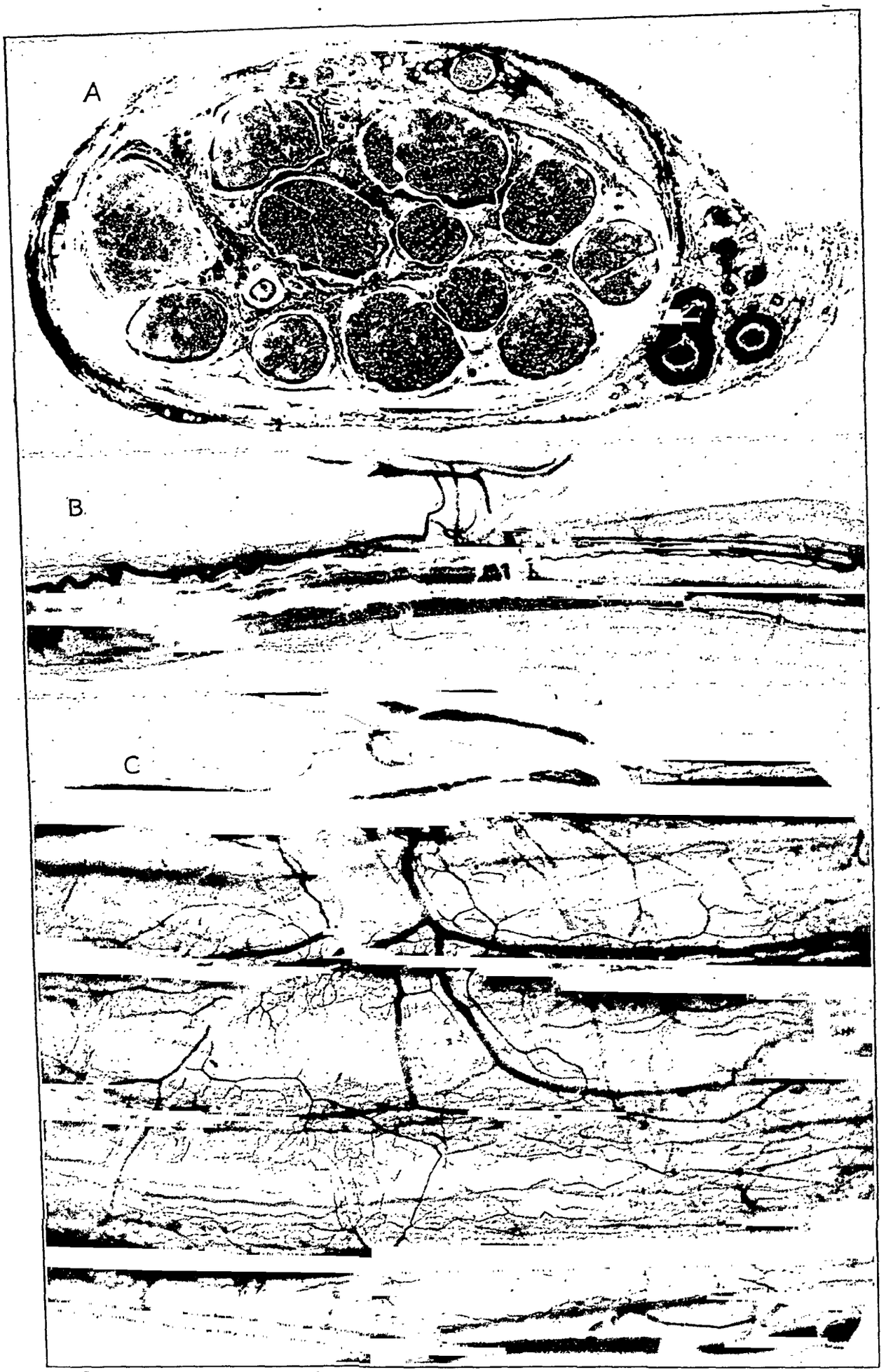

Fig. 1.—*A*; transverse section of the median nerve in the forearm, illustrating the various features of the internal architecture of the nerve. Note the thickness of the intrafascicular connective tissue septums and the position of the median artery and intraneural vessels. *B*, photomicrograph of an injected specimen; × 5. Note the relation of the arterioles and venules to one another at the site of entry into the nerve and the coarser features of their distribution within the nerve. *C*, photomicrograph of an injected specimen, demonstrating the intraneural vascular plexus; × 22.

or perifascicular sheath, and from it connective tissue septums pass into the fasciculus and subdivide it in an inconstant and irregular manner. The endoneurium, which sheathes each individual nerve fiber, is derived from these septums. According to current terminology, both the intrafascicular septums and the connective tissue sheath of the nerve fiber are to be classified as endoneurium. However, these septums are often thicker and composed of coarser fibers than the tissue surrounding the individual nerve fibers. They bring about a further refinement of the fiber pattern, and when the fasciculi divide they do so along the preformed intrafascicular septums. Surrounding the entire nerve, which is composed of a collection of fasciculi, is the external epineurium. This is a layer of areolar connective tissue, which is occasionally condensed but is more often loosely arranged. It is not always well differentiated from the surrounding mesoderm or from the open areolar tissue (internal epineurium) between the fasciculi. The external and the internal epineurium are usually referred to collectively as the epineurium, but in this paper, for reasons which will become apparent later, a distinction is drawn between them, the former being referred to simply as the epineurium and the latter as the interfascicular connective tissue.

GENERAL FEATURES OF THE EXTRANEURAL AND INTRANEURAL VASCULAR PATTERNS

As all previous investigators have pointed out, each peripheral nerve is abundantly vascularized throughout its entire length by a succession of vessels, the vasa nervorum, which, by their repeated division and anastomosis within the nerve, form an unbroken intraneural vascular net. Both the extraneural features and the intraneural disposition of the vessels were investigated, and the results in each case will be discussed separately.

EXTRANEURAL PATTERN

Classification.—Tonkoff [3a] classified the vasa nervorum into two types: arteriae nutritiae nervorum and arteriae comitantes nervorum. According to this author, the former supply the nerve and its sheaths exclusively, while the latter, though they accompany the nerve and supply it, also send branches to neighboring extraneural tissues.

Such a classification requires modification. Tonkoff did not make it clear whether the arteriae comitantes, after coursing with the nerve, terminate in it or whether their supply is predominantly to the nerve or to extraneural tissues. If the vessel is concerned principally with the supply of extraneural tissues and sends only some branches to the nerve while accompanying it, the term arteria comitans nervi is appropriate, and the branches to the nerve become true arteriae nutritiae. If, on the other hand, the vessel supplies the nerve predominantly but sends branches elsewhere before finally penetrating and terminating in the nerve, it should be regarded as an arteria nutritia nervi. Tonkoff's classification, moreover, disregards the vessels which do not accompany a nerve but which send a branch or branches to it while on their way to other structures. Such vasa nervorum could not be regarded as either arteriae nutritiae or arteriae comitantes in the sense implied by Tonkoff, yet they form a common source of nutrient vessels in the limbs. It would be preferable to retain the term arteriae comitantes as a purely descriptive term for the vessels which accompany the nerve for some distance irrespective of their participation in its vascularization.

In this paper all the vessels which enter the nerve and terminate intraneurally will be regarded as nutrient arteries irrespective of their origin and will be referred to subsequently as arteriae nervorum. The vessels which come from the main vessel of the limb, or from its named branches, and which supply the nerve exclusively will be called direct. The vessels which come from branches destined to supply extraneural tissues predominantly will be called indirect. In the limbs the vessels giving origin to the indirect type are invariably muscular or cutaneous branches. Reference to tables 1, 2, 3 and 4, in which the supply to the individual nerves has been set out, will show that indirect nutrient vessels are not commonly present. Tonkoff [3a] agreed that it is rare for nutrient arteries to come from muscular branches no matter how close they may be to the nerve. Bartholdy,[2] on the other hand, named them as a common source.

Origin.—(*a*) All investigators are agreed that the arteriae nervorum to any one nerve are derived, in an inconstant manner, from the arteries of the limb which establish an intimate anatomic relation with the peripheral nerve or which, at most, are not far distant from it. Since gross neurovascular relations in the limbs are reasonably constant, each nerve comes to be supplied predominantly from a constant group of arteries, which may include the main artery of the limb, its named branches, unnamed muscular or cutaneous branches or an anastomotic arterial loop, such as is commonly present in the neighborhood of the elbow. Thus the ulnar nerve is accompanied throughout its course by a continuous vascular pathway, formed in turn by the axillary, brachial, ulnar collateral, supratrochlear,

posterior ulnar recurrent and ulnar arteries, and it is these vessels which provide the arteriae nervorum. If there is any departure from the normal arterial pattern, then the nerve is supplied from the nearest available channel.

It has been established in this investigation that for each individual nerve there is a reasonably constant group of arteries which, by nature of their anatomic disposition, are favorably situated to supply the nerve and from which the arteriae nervorum are consequently derived. Despite the presence of this reasonably constant vascular pathway, both the number and the precise origin of the arteriae nervorum arising from the vessels composing it vary considerably, as is well illustrated in the tables 1, 2, 3 and 4, setting out the extraneural supply to the individual nerves. Not only does the extraneural pattern vary from subject to subject, as has already been pointed out by Bartholdy, but the arrangement is also asymmetric on the two sides of the body. Nevertheless, it is important to keep in mind that these variations do occur along a reasonably constant vascular pathway.

All investigators, with the exception of Quénu and Lejars, have agreed on the inconstancy of the number and origin of the arteriae nervorum. This inconstancy is such a characteristic and obvious feature that it is perhaps conceivable that when Quénu and Lejars [1b] stated "chaque tronc nerveux reçoit ses artères d'origines constantes," they had in mind not a constant formula for the arteriae nervorum themselves, but a constant system of major vessels from which the nutrient arteries took origin in serial fashion down the arm. However, there is nothing definite in their account to support such an interpretation.

(*b*) Though the site of origin is variable, there are certain regions where nerves habitually receive nutrient arteries, such as at the elbow, in the case of the ulnar nerve, and in the spiral groove, in the case of the radial nerve.

(*c*) When several arteriae nervorum arise from any one vessel participating in the formation of the accompanying vascular chain, it is unusual to see their origins evenly spaced along the present artery. On occasion there is a tendency for clustering to occur at certain points on the nerve.

(*d*) Roux [11] established certain rules relating to the branching of arteries. One of these states that "all branches which are so small that they scarcely seem to weaken or diminish the main stem come off from it at a large angle, from about 70° to 90°." In general the arteriae nervorum fall into this class and conform to this principle. Occasionally, however, it was noted that a vessel first crossed a nerve before giving off a nutrient branch, which, in order to reach the nerve, traveled in a direction opposite that taken by the parent vessel. Such recurrent branches were given off at an angle exceeding 90 degrees.

Number and Size.—All authors have agreed that the arteriae nervorum are inconstant in both number and size. Bartholdy and Petrovits and Szabo [12] (1939) denied that there is any relation between these two morphologic features, though Ramage [9] stated that when the vessels are smaller they tend to be more numerous. The results of the present investigation suggest that there is a relation between the number and the size of the arteries, and for this reason the two variables will be considered together.

(*a*) The number of nutrient arteries to any particular nerve varies considerably not only from subject to subject but on the two sides of the body. Bartholdy's[2] observation that larger nerves do not necessarily receive more vessels than do smaller nerves was confirmed in my study.

(*b*) Nerves may run considerable distances without receiving a nutrient vessel, the circulation being maintained by large descending intraneural channels. Thus, the median and ulnar nerves were seen free of entering vessels between the axilla and the elbow, nourishment over this length of the nerve being provided by large intraneural channels descending from arteries which had entered the nerve high in the axilla.

(*c*) Despite the variability in the number, site of origin and site of entry into the nerve of the arteriae nervorum, their disposition may be such, particularly in certain regions, that it is impossible to free the nerve from the surrounding tissues for more than a few centimeters without sacrificing some of the vessels supplying it.

(*d*) The caliber of the nutrient arteries fluctuates over wide limits. The largest such artery dissected in the arm measured 1 mm. in diameter, while the smallest could best be described as threadlike and required the aid of dissecting spectacles to trace it to the nerve. Bartholdy [2] stated that a diameter of 1 mm. is rarely exceeded, while the largest artery recorded by Tonkoff [3a] was 0.5 mm. in diameter. Bartholdy [2] denied that larger nerves receive larger arteries than smaller nerves. Though it is true that larger nerves do not necessarily or invariably

11. Roux, W., cited by Thompson, D. W.: On the Form and Branching of Blood Vessels, in Growth and Form, London, Cambridge University Press, 1917.

12. Petrovits, L., and Szabó, Z.: Die arterielle Versorgung der Gliedmassennerven, Anat. Anz. **88**:392, 1939.

receive larger arteries, it was observed that the largest vessels present run to the largest nerves. For example, the arteries from the perforating arteries to the sciatic nerve are conspicuous for their size. Ramage's [9] observation that the largest arteriae nervorum in the upper limb are present in the upper portion was confirmed.

(*e*) Both the size and the number must be taken into consideration when one is estimating the relative vascularity of different segments of the same nerve and of corresponding segments of different nerves. Macroscopic and microscopic investigations suggested that the two are inversely related, but no measurements were taken of the capillary bed to confirm or disprove this assumption. The important function of the arteriae nervorum is the maintenance of the intraneural vascular plexus, and this may be accomplished in a variety of ways. If a large vessel, or vessels, enters the nerve, the plexus will be maintained for a considerable distance before reenforcement becomes necessary. Thus, the median nerve has been seen extending from the axilla to the cubital fossa without receiving a single nutrient artery. Section of such a nerve reveals the presence of large descending intraneural channels derived from a vessel, or vessels, which enter the nerve in the axilla and which are sufficiently large to maintain a functionally effective pattern as far as the elbow. If, however, a small vessel enters the nerve, the process must be repeated at short intervals to achieve the same result. Consequently, under the latter conditions there is a rapid succession of many small vessels entering the nerve, though these need not be evenly spaced or of equal size. The size of the first branches to enter a nerve appears to determine the subsequent size and number of the branches entering it at more distal levels.

(f) The observation of Petrovits and Szabó [12] that the proximal portion of the nerve receives more, larger and longer nutrient arteries has not been confirmed.

(*g*) Most investigators claim that the number of arteries supplying a given length of nerve increases as the nerve passes distally. According to Bartholdy,[2] this is due to the fact that at distal levels the nerve enters regions of greater vascularity. Reference to the tables giving the number of arteries supplying the various nerves along their course shows that such an increase in number at distal levels was unusual in the case of the median nerve and was present in only approximately 50 per cent of the ulnar nerves examined.

Length.—The size and length of the arteriae nervorum were observed to be independent features, though Bartholdy [2] asserted that they were proportional to one another. The length appeared to be determined solely by the proximity of the parent vessel to the nerve—the closer the parent artery the shorter the nutrient branch.

In general, the arteriae nervorum are short, running a course of from ¼ to ½ inch (0.63 to 1.27 cm.) before reaching the nerve, but on occasion, particularly in the supply from the radial artery to the median nerve in the forearm, branches up 1 inch (2.54 cm.) in length are present.

Short, stout nutrient arteries can securely anchor a nerve to a neighboring vascular channel and render its mobilization less easy than one would expect. This, for example, is seen at the medial epicondyle and in the distal half of the forearm, where the ulnar nerve is often securely attached, in the manner described, to the ulnar collateral–posterior ulnar recurrent anastomosis and the ulnar artery respectively.

Course.—The vessels take the most direct route to the nerve and are therefore straight or gently curved; it is unusual to see them running a tortuous course. They establish contact with the nerve on that aspect which is directed toward the accompanying parent vascular channel, and only rarely on the side opposite it. These observations confirm those originally made by Bartholdy.[2]

Occasionally, however, a muscular branch, after having crossed the nerve on its way to its destination, gives off a recurrent nutrient twig, which runs back to enter the nerve on the aspect opposite that at which the direct nutrient arteries were entering. This was seen most commonly in the forearm, particularly toward the wrist, where muscular branches of the radial and ulnar arteries first crossed the median and ulnar nerves before sending a supply back to them.

Behavior of Artery on Reaching the Nerve.—Bartholdy [2] gave a detailed account of the manner in which the arteriae nervorum behave when they approach or establish contact with the nerve they are destined to supply. The results of the present investigation are represented diagrammatically in figure 2, and they are in general agreement with the observations of Bartholdy.

1. The vessel plunges immediately into the nerve without any preliminary extraneural branching. The vessel may enter at a right angle or at an acute or an obtuse angle (i. e., against the direction in which the nerve is traveling). Quénu and Lejars,[1b] on the contrary, stated that an artery never plunges directly into a nerve but always divides before penetrating it, while, in their opinion, nutrient arteries never enter the nerve at right angles.

2. The vessel turns distally on or at a varying distance from the surface of the nerve and forms a superficial descending longitudinal channel of supply which enters the nerve after a varying course or anastomoses on the surface at more distal levels with newly added vessels. Bartholdy [2] did not mention this form.

3. The vessel may descend on the surface of the nerve and then leave, giving off penetrating vessels while accompanying the nerve. Hyrtl's observation [7a] that once an artery joins a nerve it never leaves it has not been confirmed.

of a superficial longitudinal channel, from which the intraneural vessels are in turn derived, or one or both branches may behave in the manner described in section 3. In agreement with the observations of Quénu and Lejars [1b] and Tonkoff,[3a] this T-shaped division is the most common pattern assumed by a nutrient artery when it reaches the nerve.

(*c*) The vessel may divide in spray fashion adjacent to or on the nerve. The radiating branches then adopt one of the patterns already outlined. Such a pattern was recorded by Quénu and Lejars [1b] and by Petrovits and Szabó.[12]

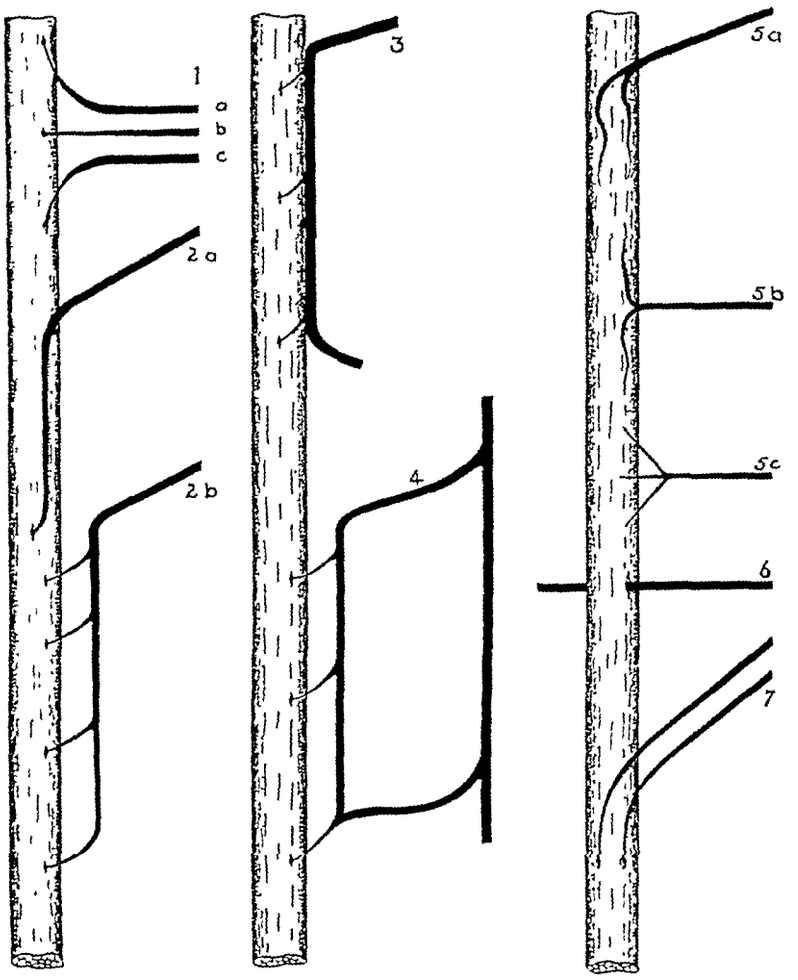

Fig. 2.—Diagram illustrating the manner in which the arteriae nervorum behave as they approach or establish contact with the nerve.

4. The nerve may be supplied from an arterial loop in the manner indicated in figure 2.

5. The nutrient artery divides on or at a varying distance from the nerve. The branches then behave as follows:

(*a*) Both branches descend on the surface, thereby outlining parallel longitudinal channels in the epineurium. It is rare to see both branches ascending on the surface.

(*b*) The branches separate to outline ascending and descending channels, which may be of equal or of unequal size—if they are unequal, the descending channel is usually, but not invariably, the larger of the two. The branches may, in turn, enter the nerve and assist in the formation

Bartholdy [2] referred to this form but stated that he had never seen it.

6. Occasionally an artery may perforate a nerve on its way to supply another structure, but, as Bartholdy has already pointed out, such a perforating vessel may or may not supply the nerve as it passes through it. Such an arrangement is commonly seen in the posterior tibial nerve in the distal third of the leg.

7. Two vessels are occasionally seen to enter a nerve at the same level.

8. When large nerve trunks run in close proximity to each other, notably in the axilla, it is common to see a nutrient artery dividing to

supply two or more nerves (fig. 3). The only other reference to such an arrangement is that made by Tonkoff.[1a]

INTRANEURAL VASCULAR PATTERN

It is common to see, particularly in the upper part of the arm, one or several longitudinally directed macroscopic vessels on the surface of a large peripheral nerve. These vessels, which are arteriolar in type, anastomose with similarly disposed vessels at more distal levels to outline a superficial vascular chain, or chains, of variable length. They run in the epineurium, and from them branches enter the nerve. Precapillaries and capillaries may enter the epineurium directly, but these vessels are too small to be detected by dissection. If present, they are more likely to be restricted to the epineurium and the interfascicular connective tissue. Transverse or oblique anastomoses may occasionally link these longitudinal channels on the surface, but, as Quénu and Lejars[1b] have already observed, they are not a feature of the pattern, and any superficial nets so outlined are large meshed. In 2 cases, however, a dense plexus was seen extending along the entire length of the ulnar nerve in the upper arm. In each instance this plexus was reenforced at frequent intervals by numerous small vessels which emerged from the muscles on which the nerve was descending. Such an anastomotic maze has also been seen on the median nerve in the forearm.

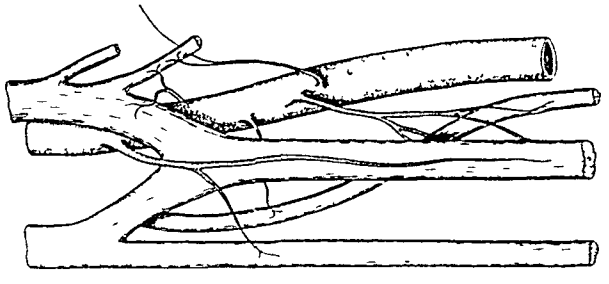

Fig. 3.—Diagram of a dissected specimen illustrating the manner in which one nutrient artery may supply more than one nerve.

A vessel, on entering a nerve, may be distributed in one of several ways. In this investigation the various intraneural patterns of division observed, irrespective of the origin of the vessel, closely resembled the patterns already described for the vessel as it approachced the nerve externally. The fanlike distribution referred to by Bartholdy[2] and by Petrovits and Szabó[12] was seen, but, as Bartholdy admitted, this arrangement is uncommon.

Bartholdy[2] expressed the opinion that if the nutrient artery enters the nerve without any preliminary extraneural branching it divides almost immediately into an ascending and a descending branch, which may be of equal or of unequal caliber; in the latter event the branch which continues in the direction of the parent channel is the larger. If, on the other hand, the nutrient artery has already divided external to the nerve, its penetrating branches undergo no further division into ascending and descending branches within the nerve but turn, following the direction in which they entered, parallel with the longitudinal axis of the nerve. Bartholdy therefore concluded that every nutrient artery, before breaking up into its finer branches, divides at least once, inside or outside the nerve, into an ascending and a descending branch. I have been unable to confirm such a generalization.

From these penetrating arterioles are derived the intraneural arterioles, precapillaries and capillaries which, by their repeated division and anastomosis, outline a continuous longitudinal intraneural vascular net which extends the length of the nerve (fig. 1 *B* and *C*). Holl[13] (1880), Zuckerkandl[14] (1885), Makins[15] (1919) and others described the occasional utilization of this longitudinal intraneural anastomosis in the establishment of a collateral circulation in the limbs.

It is rare for an arteriole on entering a nerve to plunge immediately into a fasciculus—a feature which did not escape the notice of Quénu and Lejars.[1b] In general the smaller penetrating arterioles rapidly diminish in size and are soon lost in the intraneural plexus. The larger arterioles, on the other hand, descend in the interfascicular spaces and retain their identity and dimensions, despite repeated branchings, over varying, but often extensive, lengths of the nerve before they are in turn finally absorbed in the plexus or are reenforced by a newly entering vessel. They may pursue a vertical, oblique, irregular or mildly tortuous course as they descend. The branching of these penetrating arterioles in the interfascicular tissues results in the formation of a series of longitudinally disposed channels, arteriolar or precapillary in type, which are linked at irregular intervals by transverse or oblique anastomoses. These epineurial and interfascicular arterioles and precapillaries represent the largest vessels observed in the nerve and form the basis of the intraneural vascular pattern.

13. Holl, M.: Verrenkung des linken Ellbogengelenkes mit Zerreissung der A. ulnaris und der N. medianus und ulnaris, Med. Jahrb. **10**:151, 1880; cited by Tonkoff.[3]

14. Zuckerkandl, O.: Zwei Fälle von Collateralkreislauf, Med. Jahrb. **15**:273, 1885; cited by Tonkoff [3a]; cited by Poirier, P., and Charpy, A.: Traité d'anatomie humaine, ed. 2, Paris, Masson & Cie, 1909, vol. 3, p. 633.

15. Makins, G. H.: Gunshot Injuries to Blood-Vessels, Bristol, J. Wright & Sons, 1919.

From them, finer branches pass directly into the fasciculi, or to the perineurium, from which they subsequently enter the fasciculi. These branches, which are capillary and precapillary in type, are, in turn, longitudinally disposed in these situations. Capillaries predominate in the fasciculus and precapillaries in the perineurium; the terminal intrafascicular capillary meshwork is established by their repeated branching and anastomoses. Inside the fasciculus the vessels are localized to the intrafascicular connective tissue septums. The statement by Adams [16] that the capillary plexuses alone extend into the endoneurium is incorrect (fig. 4 *C*).

Thus it is customary to find four systems of vessels disposed parallel with the longitudinal axis of the nerve. The vascular systems in the epineurium and in the interfascicular tissues are composed of arterioles and precapillaries, while the vessels in the perineurium and in the fasciculi are composed of capillaries and precapillaries. These longitudinally directed channels repeatedly give off side branches, more or less at right angles, in all directions at frequent, but irregular, intervals. These branchlets, in turn, divide and redivide in a similar manner and finally anastomose to give a terminal vascular net composed of rectangular meshes, which tend to be alined in the longitudinal axis of the nerve.

Serial histologic sections demonstrate that the number, size and position of the longitudinally directed interfascicular vessels vary from one level to another. One or several vessels may be noted in this situation (fig. 4 *A*, *B* and *C*). When several vessels are present, one is usually larger than the others. The relation between size and number observed in the extraneural distribution also obtains for the interfascicular arteriolar pattern. Thus, there may be one large interfascicular arteriole, many small ones or a combination of vessels of varying size.

Observations suggest that the larger the nerve trunk the larger are the arterioles it carries.

No single vessel was observed to dominate the pattern over the entire length of the nerve. In the case both of the median and of the ulnar nerve a large vessel, located on the inner surface of the nerve, has occasionally been observed descending from the axilla to the elbow without interruption and without any alteration of position. This must be regarded as uncommon, for it is more usual for the major intraneural channel of one segment to be replaced as the nerve descends by a newly entering arteriole.

16. Adams, W. E.: The Blood Supply of Nerves: II. The Effects of Exclusion of Its Regional Sources of Supply on the Sciatic Nerve of the Rabbit, J. Anat. **77**:243, 1943.

The variation in number of the interfascicular arterioles is due to the repeated division of a large arteriole or to the entrance of new vessels. Both factors influence the number of vessels present at any particular level. However, it was not possible to ascertain with certainty whether the site of redistribution of the nerve fibers and the formation of additional, but smaller, fasciculi are related to the site of entry of new vessels or to the division of vessels already contained with the nerve (fig. 5).

The variation in position is determined not only by the entrance of new vessels but by the alteration in position of interfascicular vessels already descending in the nerve. Such an alteration in position appears to be influenced to some extent by the regrouping of the nerve fibers, which results in a modification of the intraneural fascicular pattern (fig. 5).

There is a general tendency, as Ramage [9] originally pointed out, for the largest vessels to be arranged toward the center of the nerve in the forearm and at the periphery in the upper arm. There are exceptions to such a generalization (fig. 4 *A* and *B*), the most notable being the median artery, which usually descends on the surface of the median nerve in the forearm.

Though the interfascicular arteriolar pattern varies from level to level, from side to side and from subject to subject, the manner of formation and the structure of the terminal intrafascicular capillary meshwork strongly suggest that the blood supply to individual nerve fibers is, on anatomic grounds at least, substantially the same.

As the nerve branches, the vascular net behaves accordingly, and a vascular net commensurate with the size of the branch separates with it. The neural and vascular divisions are often seen for some distance proximal to the point where actual separation takes place. It is to be noted, also, that after the branches of nerves have completely separated from the parent nerve they may receive separate nutrient arteries.

The manner in which the intraneural pattern is maintained and reenforced is of fundamental importance. A characteristic feature is the considerable overlap of supply which obtains between nutrient arteries entering the nerve at different levels. This makes it extremely difficult to determine how much of a nerve is supplied by a single nutrient artery. The arrangement seems to be such that no vessel can be said to supply a precise and discrete segment of a nerve, as some authors have claimed. Petrovits and Szabó [12] alone described the arteriae nervorum as "end arteries." Other authors, however, while admitting the existence

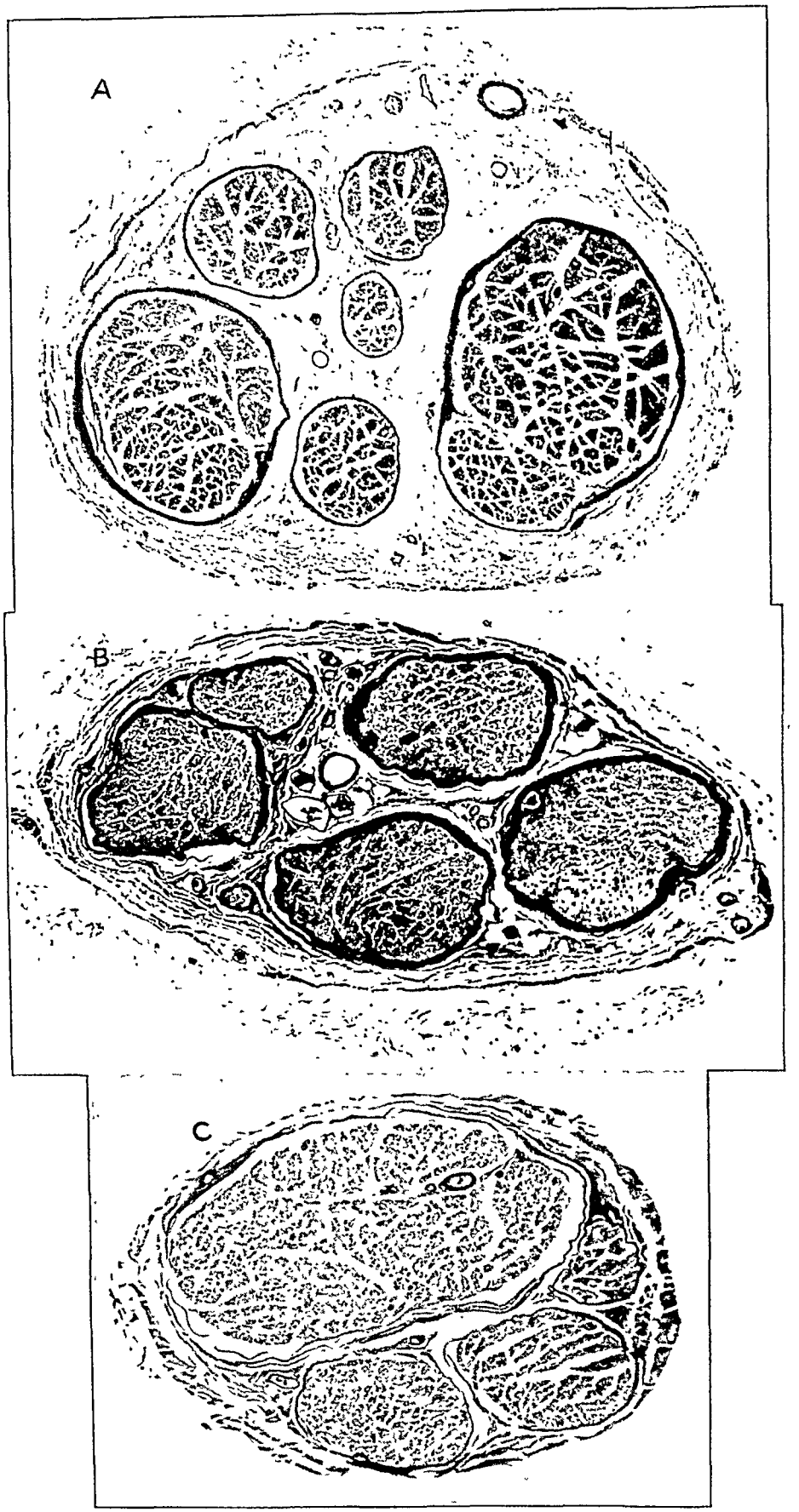

Fig. 4.—*A*, transverse section of the median nerve in the upper arm; ×29. Note the relation of the vessels to the components of the nerve and the presence of a peripherally situated major arteriole. *B*, transverse section of the ulnar nerve in the upper arm; ×38. Note the relation of the vessels to the components of the nerve and the presence of a centrally situated major arteriole. *C*, transverse section of the ulnar nerve in the upper arm; ×27. Note the presence of a large precapillary inside a fasciculus.

of longitudinal anastomosing channels, stated that each nutrient artery dominates the intraneural circulation in its own region. Whether or not this is so remains to be established by experimental investigations into the functional significance of the supply. The physiologic evidence at present available is inconclusive. Adams [16] recently investigated the effects of exclusion of the regional sources of the vascular supply on the sciatic nerve of the rabbit. He

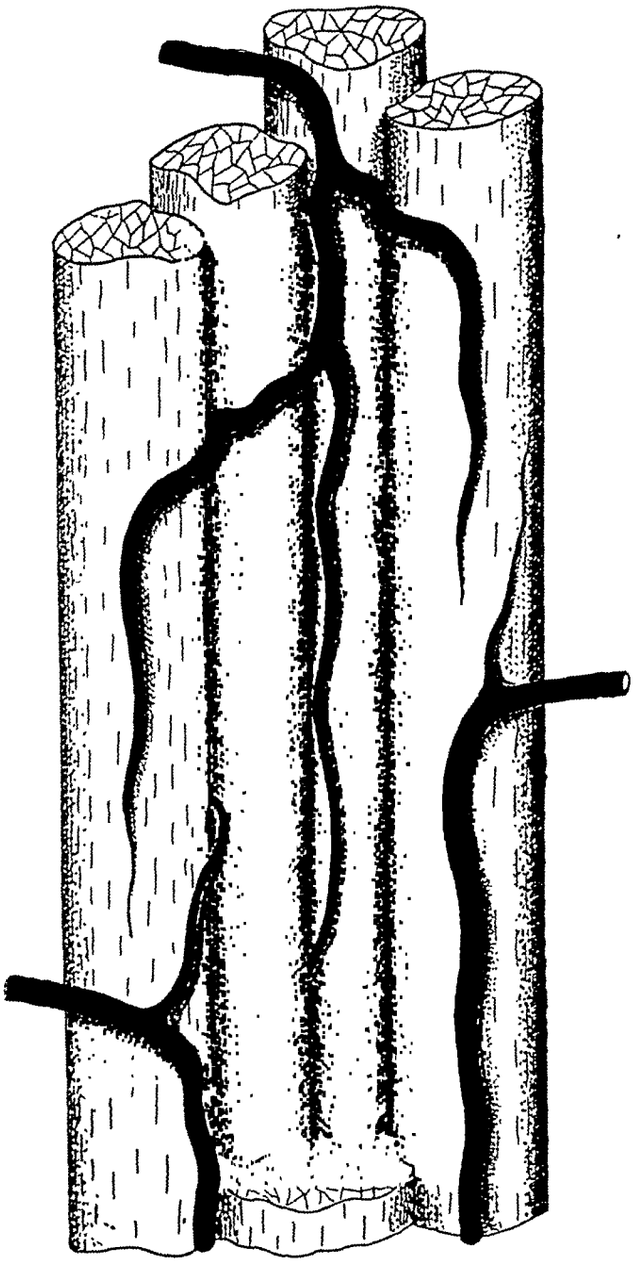

Fig. 5.—Diagram illustrating the manner in which the number, size and position of the intraneural arterioles vary along the course of the nerve.

claimed that such exclusion resulted, in all but 2 cases, either in no or in limited and insignificant degeneration. In the 2 cases extensive degeneration occurred, but Adams was uncertain whether this was to be attributed to manipulation of the nerves or to a variation in their intrinsic vascular pattern. Both the overlap and the profuse and extensive character of the anastomoses render such a conception extremely unlikely. Admittedly, there are instances, though they are uncommon, in which one vessel supplies long stretches of a nerve without reenforcement, but it has been demonstrated in sectioned and injected material that even under such apparently adverse conditions of supply the anastomosis is of such dimensions at the peripheral limits of the solitary channel that segmental ischemia due to the blocking of such a single vessel is a remote possibility. During this study nerves were frequently stripped at operation of all surrounding connections for distances up to 10 cm., yet when the nerve was divided distally, the cut end of the freed segment continued to bleed profusely. The results may be serious, however, if all the vessels to the nerve are affected simultaneously in a generalized sclerosing condition. The establishment of an effective collateral circulation is then no longer possible, and the conducting elements consequently suffer. Again, compression of a length of nerve by a pressure exceeding the arterial pressure prevents blood from entering the compressed segment. Under these conditions, however, it is difficult to determine whether the effects of such an experimental procedure are due to the local ischemia or to the pressure whereby it is produced.

VEINS

Quénu and Lejars [1b] alone carefully examined the venous drainage of the peripheral nerves. They studied in turn, the veins of the cutaneous nerves, the veins of the deep nerves and the veins of the nerve plexuses and recorded the following observations:

1. The main cutaneous nerves almost always accompany a large subcutaneous vein. Nevertheless, the veins of the cutaneous nerves drain predominantly into muscle veins beneath the deep fascia. These authors claimed that any drainage to the subcutaneous venous system is insignificant.

2. The veins of the deep nerves always drain to muscular veins or to the venous plexus in the wall of a neighboring artery. They never drain to the principal vein, or veins, accompanying the artery. Quénu and Lejars claimed to have demonstrated an intimate relation between the veins of the muscles and the veins of the nerves by which the two form a neuromuscular venous system. They attributed a functional significance to this arrangement and claimed that the muscular contractions which aid the venous drainage of the muscles automatically aid the venous drainage of the nerves.

3. The veins draining the nerve plexuses empty into collateral venous channels which have

a muscular origin. It is claimed that the neuromuscular venous relations are the same as venous relations described for the large peripheral nerves in the limbs.

4. The mode of emergence of veins from the nerve and the intraneural venous pattern correspond essentially to the arterial arrangement. The arteries and the veins enter and leave together.

The following additional observations were made in the present investigation:

1. Venules are the largest venous vessels seen in and leaving the nerve.

2. In general, the structure of the intraneural venous pattern corresponds to the arterial arrangement. Venules and arterioles do not always run together, however, either inside or outside the nerve, while counts suggest that the number of interfascicular venules slightly exceeds the number of arterioles.

3. Bichat [6] claimed that in the larger nerves the emerging veins bear a resemblance to the cerebral veins in that they leave the nerve independently of the entering arterioles. This arrangement, though commonly seen, is by no means invariable, for veins and arteries frequently leave and enter the nerve at the same time.

4. The number of venules leaving the nerve does not always correspond with the number of arteries entering the nerve.

5. It is not uncommon to see two veins emerging from the nerve, one on each side of an entering artery.

6. Though the mode of termination of veins from deep nerves, as described by Quénu and Lejars, is common, large emerging veins have been repeatedly seen entering the principal veins.

7. Observations on the venous drainage of the cutaneous nerves have been limited, but they suggest that, though the arrangement described by Quénu and Lejars is the more usual, a drainage into the subcutaneous venous system is not as uncommon as they claimed.

BLOOD SUPPLY OF THE MEDIAN, ULNAR AND RADIAL NERVES

Though the papers of Quénu and Lejars,[1b] Bartholdy,[2] Tonkoff [3] and Bourguet [17] all contain references to the blood supply of individual peripheral nerves, these reports lack the detail provided by Ramage,[9] who confined his investigation to an examination of the blood supply to the large peripheral nerves in the upper limb. The results of the present study will first be described and then compared with the observations previously reported.

MEDIAN NERVE

The source and number of the arteriae nervorum in the dissected specimens are set out in table 1. The supply recorded as coming from the axillary artery includes the vessels which reached the nerve, not directly, but by descending along one or both roots.

Axilla and Upper Portion of Arm.—The nerve was accompanied as far as the elbow by an arterial channel composed of the axillary and brachial arteries, both of which supplied the nerve. The axillary artery constantly supplied the nerve, either directly or on occasion, from its acromiothoracic, lateral thoracic and subscapular branches. In only 1 case did the brachial artery fail to supply it. Toward the lower part of the upper portion of the arm branches were also occasionally received from the ulnar collateral and supratrochlear arteries.

In 20 of the 37 specimens the nerve received from a variable source, but usually from the axillary artery itself, a large nutrient twig into the forked union of the two roots. This nutrient artery formed the subject of a paper by Robinson [18] (1910), in two thirds of whose series of cases it was present. He described the vessel as extending in some cases as far as the elbow without any reenforcement. This was seen only once in my series. Tonkoff is the only other investigator to mention the "arteria nutritia nervi mediani prima," and he attached great importance to it.

Ramage [9] listed arteriae nervorum coming from the axillary (inconstantly, one to two branches), the brachial (constantly, one to four branches) and the supratrochlear (occasionally, one branch) artery and/or their branches. Bartholdy [2] gave the supply as coming from the axillary, brachial (five to ten branches), bicipital and supratrochlear arteries. Tonkoff claimed that the supply is derived from the axillary, brachial (one to four branches), bicipital (frequently one branch) and supratrochlear (one to two branches) arteries. Quénu and Lejars [1] stated that the median nerve receives branches from the brachial and the supratrochlear artery. They gave no details but stated that the supratrochlear almost always sends it a branch. According to Bourguet, the brachial artery gives off only a small number of branches to the nerve in the

17. Bourguet, M.: Des vasa nervorum, Compt. rend. Soc. de biol. **77**:656, 1913.

18. Robinson, R.: Les vaisseaux de la fourche du nerf médian, Compt. rend. Acad. d. sc. **151**:535, 1910.

upper part of the arm, and these branches have long intraneural courses. He expressed the belief that almost the entire brachial portion of the nerve is nourished by a single nutrient artery. In the light of the present observations and results of other investigators, this must be regarded as being unusual.

Cubital Fossa.—In the cubital fossa the nerve was related to the termination of the brachial artery, the first part of the radial and ulnar arteries and the common interosseous, anterior interosseous and anterior ulnar recurrent arteries. Nutrient vessels to the nerve were traced from one or more of these arteries or their branches.

Forearm.—No artery constantly supplied the nerve in the forearm. Vessels were traced to the nerve from the ulnar, radial, common interosseous, anterior interosseous and median arteries, and occasionally also from their muscular branches.

In the forearm the median nerve descends with the radial and ulnar arteries well to its lateral and medial sides respectively and with the anterior interosseous artery on a deeper plane. Thus the vascular relations are not so intimate as in the upper arm, but this lack of a suitably placed major limb artery is frequently compensated for by the presence of the median artery, which accompanies the nerve down the foreram. This investigation confirmed Tonkoff's observation that the nutrient arteries in the forearm vary in number with the development of the median artery, which supplies the nerve exclusively if it is strongly developed. This vessel, which was present in 27 specimens, may take origin from the ulnar, the common interosseous, the anterior ulnar recurrent or the anterior interosseous artery or one of their large muscular branches. In this series it conformed to one of two basic types. In the majority of cases (17 out of 27) it terminated by entering the nerve after pursuing a course of variable length on or near its surface. In the remaining cases the vessel did not enter the nerve but ran on or adjacent to it before finally entering the hand or the flexor muscles on the distal part of the forearm. As the median artery descended on or near the nerve, it gave one or more branchlets to the nerve before finally penetrating or leaving it. Ramage stated the opinion that each branch of the median

TABLE 1.—*Arterial Supply of the Median Nerve*

	Axillary		Brachial		Ulnar Collateral	Supratrochlear	Ulnar	Common Interosseus	Anterior Ulnar Recurrent	Median	Radial	Indirect Supply to Forearm, Origin Unknown
	Direct *	Indirect	Direct	Indirect								
1 Left	3	—	1	1	—	—	—	—	1	1	—	—
Right	4	—	7	1	—	1	—	—	—	1	2	1
2 Left	3	—	4	1	—	—	2	—	—	1	4	—
Right	1	—	5	—	—	—	—	—	—	—	1	2
3 Left	3	—	3	—	—	—	1	—	—	1	1	—
Right	1	—	3	—	—	—	5	—	—	—	—	4
	1 A-Th.											
	1 L.Th.											
4 Left	3	—	5	—	—	—	2	—	—	1	—	—
Right	1	1	2	1	—	—	1	—	1	—	1	—
5 Left	2	1	1	1	—	—	—	—	1	—	—	—
Right	1	4	2	1	—	—	—	—	—	1	1	—
6 Left	2	—	6	—	—	—	—	—	—	1	—	—
Right	3	—	2	1	1	1	—	—	1	1	—	—
7 Left	3	—	—	—	—	2	—	—	—	1	—	2
Right	3	—	1	—	—	—	—	—	—	1	1	—
8 Left	1	—	3	—	—	—	—	—	—	1	—	4
Right	2	—	2	1	—	—	—	—	—	—	3	2
9	1	—	1	2	3	—	1	3	—	1	3	3
10	3	—	2	—	—	—	1	—	1	—	—	2
11	3	—	4	—	—	1	2	—	—	1	1	2
12	1	—	5	—	—	—	1	—	—	1	—	—
	1 A-Th.											
13	2	—	7	1	—	—	—	—	—	1	1	—
	1 L.Th.											
14	2	1	4	—	—	—	—	—	—	1	—	—
15	1	—	4	—	—	—	—	—	—	1	—	—
16	2	—	5	1	—	—	—	—	—	1	—	1
17	3	—	3	1	—	—	—	—	—	1	2	1
18	1	—	5	1	—	2	—	—	—	—	—	2
19	—	1	3	4	—	—	1	—	—	—	—	—
20	5	—	8	—	—	—	—	—	—	1	4	—
	1 Subs.											
21	—	1	5	—	—	—	—	—	—	1	1	—
22	1	—	4	—	—	—	—	2	—	—	1	—
23	1	—	6	1	—	—	—	—	—	1	2	—
	1 Subs.											
24	3	—	2	—	—	1	—	—	—	1	1	—
25	2	—	1	—	2	—	3	—	—	—	—	—
26	1	—	4	—	—	—	—	—	—	1	1	—
27	3	1	3	—	—	—	1	—	—	1	1	—
28	2	1	5	1	—	—	—	—	2	1	1	—
29	2	1	10	—	—	—	—	—	—	1	1	—

* A-Th. indicates the acromiothoracic; L.Th., the lateral thoracic, and Subs., the subscapular artery.

artery to the nerve is a separate nutrient vessel. It is preferable, however, and more in keeping with the basic nature of the supply, to regard this vessel and any branches it may give to the nerve externally as a single nutrient system. Arrangements such as have been described for this channel are frequently present elsewhere in the limb and have already been described as types 2 and 3 in the previous section, which deals with the behavior of the nutrient vessel on its approaching the nerve (fig. 2). Since in these positions the nutrient artery and its branches have been considered as a single channel, there can be no justification for departure from this practice in the case of the median artery.

In 3 of 10 specimens in which the median artery was absent the nerve received its last nutrient artery in the cubital fossa.

At the wrist, the radial and ulnar arteries come slightly closer to the nerve as the forearm narrows, and this is the region where these vessels or their branches most commonly supply the median nerve.

Ramage listed arteriae nervorum coming inconstantly from the radial (one to four branches), ulnar (one to four branches), anterior ulnar recurrent (one to two branches), anterior interosseous (one to three branches) and median arteries, and in 1 specimen the nerve received a single branch from the superficial volar artery. Bartholdy gave the supply as coming from the radial and ulnar arteries, from the anastomoses of these two arteries and from the anterior ulnar recurrent, anterior interosseous and median arteries. According to Tonkoff, the supply in the forearm is derived from the "cubital," ulnar, anterior ulnar recurrent and median arteries, from the muscular branches of the anterior interosseous and radial arteries and from the anastomoses between the radial and the ulnar artery. Quénu and Lejars [1] described branches coming from the anterior ulnar recurrent, radial and median arteries. Bourguet stated that the ulnar artery sends a special branch to accompany the nerve, from which a series of arteriae nervorum arise, each of which has a limited area of distribution in the nerve. Such a localized distribution has not been confirmed.

Comment. — There is, among investigators who have submitted the arterial supply to a detailed examination, general agreement concerning the vessels from which the arteriae nervorum are derived. All are of the opinion that the supply from the brachial artery predominates in the upper arm. This is only to be expected when one considers that the vessel accompanies the nerve throughout its course in this region.

In general the number of nutrient arteries recorded in this investigation as reaching the nerve in the upper portion of the arm exceeds the number given by either Ramage or Tonkoff. The figures correspond with those reported by Bartholdy. Though large nutrient arteries are seen in the forearm, the largest observed, with the exception of the median artery, usually occur in the upper arm.

Ramage's observation that the number passing to the nerve in the forearm exceeds the number reaching it in the upper arm has not been confirmed. The variable size of the median artery and the irregular manner in which it supplies the nerve and terminates in relation to it, however, render difficult any comparison between the number of vessels received in the upper arm and that received in the forearm. For reasons already set out, it is proposed, unlike Ramage, to regard the median artery and its arteriae nervorum as a single nutrient system. In this investigation it has been determined that even if the branches of this artery to the nerve are regarded as separate nutrient vessels, the number received by the nerve in the upper arm would, in the majority of cases, still exceed the number received in the forearm. There seems no doubt that the smaller number of nutrient arteries received in the forearm is due to the absence of large neighboring channels of supply. As has already been pointed out, this is compensated for by large descending intraneural vessels or by the addition of a specific nutrient vessel, the median artery, which in the majority of cases in which it is present ends within the nerve. It is to be stressed, however, that the number of vessels passing to a nerve is, in the absence of additional data, of little significance in estimating the blood supply of that nerve, and studies devoted to this feature alone are likely to be misleading.

It is interesting to note the higher incidence of the median artery in fetal, as opposed to adult, material in Ramage's series.

ULNAR NERVE

The ulnar nerve is accompanied throughout its course by a continuous arterial chain derived, in turn, from the axillary, brachial, ulnar collateral, supratrochlear, posterior ulnar recurrent and ulnar arteries. It is from this arterial system that the blood supply of the ulnar nerve is derived. The source and number of the arteriae nervorum are set out in table 2. In this table the supply recorded as coming from the axillary artery includes the vessels which passed

to the medial cord of the plexus and which could be traced distally into the ulnar nerve. Though it is possible to predict with some degree of certainty from which vessels the supply will be derived, it is not possible to foretell, as is clearly brought out in table 2, how many arteriae nervorum the nerve will receive, the numerical contribution of each individual vessel in the system or at what point they will branch from the parent vessel.

Axilla and Upper Portion of Arm.— In this region the axillary artery or its branches constantly supplied the nerve, as did the ulnar collateral artery in every case. According to Bartholdy the nerve is supplied from the axillary artery, the brachial artery and its muscular branches and the ulnar collateral artery. The latter stated that as long as the nerve is near the brachial artery it is supplied from its muscular branches, and only rarely directly from the artery itself, but this is an observation that has not been confirmed by any other investigator. On the other hand, his observation that there are long stretches of the nerve in the upper arm which do not receive any arteries has been confirmed. Ramage in 25 specimens listed the nerve as being supplied by the

TABLE 2.—*Arterial Supply of the Ulnar Nerve*

	Axillary		Brachial		Pro-		Ulnar Collateral		Supra-	Posterior Ulnar Recurrent		Ulnar	
	Direct*	Indirect	Direct	Indirect	funda	Radial	Direct	Indirect	trochlear	Direct	Indirect	Direct	Indirect
1 Left	3	—	1	—	—	—	—	—	1	2	—	10	—
Right	4	—	1	—	—	—	2	6	—	2	—	8	1
2 Left	2	—	—	1	—	—	7	—	—	4	—	15	—
Right	1	—	1	—	—	—	4	—	—	2	—	15	—
3 Left	1 Subs.	—	—	—	—	—	2	—	1	2	—	6	—
Right	3	—	—	—	—	—	4	—	—	2	—	3	—
4 Left	2	—	1	—	—	—	2	—	2	3	—	4	2
Right	1 Ach	—	—	—	—	—	4	—	—	2	—	5	—
5 Left	1	—	2	—	—	—	1	—	2	1	—	4	—
Right	1	2	1	—	—	—	3	1	—	3	—	5	1
6 Left	3	—	2	—	—	—	1	—	1	3	—	6	—
Right	3	—	—	1	—	—	5	—	—	3	—	5	—
7 Left	1	—	—	—	—	—	2	—	—	2	—	2	—
Right	2	—	—	—	—	—	4	—	—	2	—	4	—
8 Left	1	1	1	—	—	—	4	—	—	2	—	5	—
Right	1	—	—	—	—	—	3	—	—	1	—	7	—
9	2	—	—	—	—	—	1	—	—	3	—	6	—
10	1	—	—	—	—	—	2	5	—	2	—	8	—
11	2	—	—	—	—	—	5	—	—	4	—	8	—
12	1	—	1	1	—	—	3	—	—	2	—	8	—
13	2	—	2	2	—	—	4	—	—	2	1	6	—
14	1	—	3	—	—	—	2	—	2	1	—	6	—
15	1	—	—	—	—	—	3	—	—	1	—	8	—
16	1	—	—	—	—	3	5	—	—	4	—	12	—
17	—	1	—	—	—	—	3	—	—	1	—	4	—
18	1 Subs.	—	—	—	2	—	1	—	1	1	—	4	—
19	2	—	—	2	—	—	1	—	1	2	—	1	—
20	3	1	—	—	—	—	2	—	—	1	—	6	—
21	2	—	—	—	—	—	4	1	—	1	—	1	—
22	1 Subs.	—	—	—	—	—	4	—	2	2	—	4	—
23	1	—	—	—	—	—	5	—	1	1	—	5	—
24	2	1	—	—	—	—	2	—	3	2	—	7	—
25	2	—	—	—	3	—	2	—	4	2	—	1	—
26	1	—	—	—	—	—	4	—	2	1	—	4	—
27	3	—	1	—	—	—	2	—	1	1	—	1	—
28	—	1	—	—	—	—	1	—	1	1	—	3	—
29	1	—	1	—	—	—	6	—	2	2	—	2	—

* Ach indicates the anterior circumflex humeral, and Subs., the subscapular artery.

lateral artery in every specimen but one, while the brachial and supratrochlear arteries supplied it only irregularly. In the majority of specimens the main source of supply was from the ulnar collateral artery. When nutrient branches from this vessel were absent or few the nerve was nourished by large channels descending intraneurally from the axilla. Occasionally the arteria profunda brachii and a high radial artery obtained a sufficiently intimate relation to the nerve to supply it.

Tonkoff described arteriae nervorum from the axillary and ulnar collateral (one to four branches) arteries, with an occasional one from a muscular branch of the brachial artery. He attributed the main supply to the ulnar collateral ulnar collateral artery (one to four branches) in every specimen and by the axillary artery in all but 2 specimens (one direct branch from the main trunk in 21 specimens and one branch from the subscapular artery in 2 specimens); a supply was also derived inconstantly from the supratrochlear artery (one to two branches) and very occasionally from the brachial (one branch in 5 specimens and two branches in 1 specimen) and the profunda (one branch in 3 specimens) artery.

Region of the Medial Epicondyle.—Attention is drawn to the constant blood supply received by the nerve in the vicinity of the medial epicondyle. The ulnar collateral, supratrochlear and posterior ulnar recurrent arteries participate in the formation of an anastomotic system which is closely

associated with the nerve as the latter curves around the medial epicondyle. The nerve may be firmly anchored in this position by short nutrient arteries passing directly to it from the anastomotic channel, and these vessels must be sacrificed to permit adequate mobilization of the nerve when it is being transplanted anterior to the epicondyle. This anastomosis is often of such dimensions that it is difficult to determine where one vessel ends and another begins. Consequently it is difficult at times to ascertain from which particular artery a nutrient vessel is taking origin. The figures given are as accurate as the investigation permitted.

Tonkoff described one to three branches entering the nerve from this anastomosis. Bartholdy noted in his series that the vessels to the nerve were exceedingly well injected in this region, though in his account he mentioned only a supply from the posterior ulnar recurrent artery and from a muscular branch to the flexor carpi ulnaris muscle.

Forearm.—From the medial epicondyle to the wrist the nerve is accompanied in turn by the posterior ulnar recurrent and the ulnar artery, and these vessels, particularly the ulnar, send many nutrient arteries to the nerve. The ulnar artery is usually closely applied to the nerve in the distal one half to two thirds of the forearm, and the arteriae nervorum are consequently short and pass directly into the nerve.

Tonkoff described a branch from the posterior ulnar recurrent artery or its muscular branches in the upper third of the forearm and two or three branches from the ulnar artery or its muscular branches in the distal two thirds of the forearm. According to Ramage, the nerve in the forearm is supplied constantly from the posterior ulnar recurrent (one to three branches) and the ulnar (one to seven branches) artery. He gave a higher incidence of indirect nutrient branches from the latter than was recorded in the present investigation. Bartholdy claimed that the nerve is always supplied by the ulnar artery at 2 cm. intervals. This regularity was seen on occasions, but it was certainly not a feature of the supply.

Comment.—There is general agreement concerning the vessels from which the arteriae nervorum take origin. All investigators are of the opinion that in the upper arm the nerve is supplied principally by the ulnar collateral artery and that in the forearm a large number of arteriae nervorum are received from the posterior ulnar recurrent and ulnar arteries. In general the number recorded in the present investigation as reaching the nerve in the upper arm exceeded that given by Ramage and by Tonkoff. The number of indirect arteriae nervorum observed in the forearm was less than that reported by Ramage.

As in the case of the median nerve, the figures presented by Ramage indicate that the number of nutrient arteries passing to the ulnar nerve in the forearm invariably exceeds that reaching it in the upper arm. The present investigation showed, however, that the number of nutrient arteries to the nerve in the forearm as compared with the number to the nerve in the upper arm was as follows:

No. of Nutrient Arteries	No. of Specimens
Equal	3
Greater in the forearm	18
Greater in the upper arm	16

The number received, however, was subject to such extreme ranges of variation that it is believed that any generalization on the data available would be misleading.

RADIAL NERVE

The radial nerve is supplied by the axillary, brachial and profunda brachii arteries and their branches as far as its entry into the spiral groove, by the profunda brachii artery while running in the groove, and, finally, by the anastomosis between the profunda brachii and the anterior radial recurrent artery. This anastomosis is closely related to the nerve as it descends in the intermuscular furrow between the brachialis muscle, medially, and the muscles arising from the supracondylar line, laterally. The source and number of the nutrient arteries in the various regions are set out in table 3.

Ramage, in his account, provided no information concerning the site where the arteriae nervorum take origin from the profunda artery. For this reason, it is convenient to refer to his observations here rather than in the sections relating to the regional supply. In a study of 25 specimens he listed the nerve as being supplied by the following arteries: axillary (one branch in 7 specimens); subscapular (one to two branches, in 12 specimens); brachial (one to two branches, in 16 specimens); profunda (two to nine branches, in 25 specimens), and anterior radial recurrent (one to three branches, in 14 specimens. Thus the profunda artery alone constantly supplied the nerve and also provided the largest number of nutrient arteries. According to Ramage, the arteriae nervorum from the brachial artery were predominantly indirect and took origin from muscular branches.

Axilla; Arm.—Information concerning the number of arteriae nervorum received from the

axillary, subscapular, brachial and profunda brachii arteries is provided in table 3. The supply recorded as coming from the axillary artery includes the vessels which entered the posterior portion of the cord and which could be traced distally into the radial nerve.

In this region Tonkoff described a constant supply from the subscapular artery, in addition to arteriae nervorum from the profunda artery and/or its muscular branches. He did not mention either the axillary or the brachial artery. Ac-

TABLE 3.—*Arterial Supply of the Radial Nerve**

	Axillary		Brachial, Direct	Profunda		Furrow	Anterior Radial Recurrent	
	Direct	Indirect		Arm	Groove		Direct	Indirect
1 Left.....	2	—	—	—	2	—	—	2
Right.....	4	—	1	—	5	—	1	2
2 Left.....	1 *	—	2	—	4	2	1	—
Right.....	1	—	1	—	2	1 Ind.	2	—
3 Left.....	1	—	—	1	1	2	1	—
Right.....	2	—	—	—	6	3	1	2
4 Left.....	2	—	—	—	3	—	1	1
Right.....	1	—	—	—	4	—	2	—
5 Left.....	1 *	1	—	—	3	1	2	1
Right.....	3 *	—	—	—	4	—	1	—
6 Left.....	3	—	—	—	4	2	2	—
Right.....	1 *	—	—	—	3	—	2	—
7 Left.....	2	—	—	—	5	—	1	—
Right.....	2	1	—	—	4	1	1	—
8 Left.....	2	—	—	—	3	1	1	—
Right.....	1	—	—	1	2	1	—	—
9.....	1	—	—	1	3	2	—	1
10.....	2	—	—	—	3	1 Ind.	1	—
11.....	1	—	—	—	2	—	2	—
12.....	2 *	—	—	1	1	2	—	—
13.....	1	—	1	—	1	2	2	—
14.....	1							
	1 *	1	—	—	4	2	1	—
15.....	1 *	—	—	1	2	—	1	1
16.....	2	—	—	—	9	—	—	—
17.....	1	—	—	—	1	2	1	—
18.....	1 *	—	—	1	2	1	—	—
19.....	1	—	—	1	1	1	1	—
20.....	1 *	—	—	1	1	1	—	—
21.....	2	—	—	—	3	1	—	—
22.....	1 *	—	—	—	3	1	1	—
23.....	1 *	—	—	—	1	1	2	—
24.....	2	—	—	1	3	1	1	—
25.....	1	—	1	1	4	3	—	—
26.....	1							
	1 *	1	—	1	1	2	1	—
27.....	2							
	2 *	—	—	—	1	1	—	—
28.....	1 *	—	1	—	2	1	1	—
29.....	1	1	2	—	3	3	—	—

* Indicates subscapular artery, and Ind., here and in table 4, indirect blood supply.

cording to Bartholdy the arteriae nervorum are derived from the axillary, profunda and brachial arteries. He stressed the predominance of the supply from the muscular branches of the brachial artery, with which Ramage expressed agreement, but this observation is contrary to the results of the present investigation.

Spiral Groove.—The profunda artery constantly supplied the nerve in this situation. Tonkoff, Bartholdy, Bourguet and Ramage referred to the blood supply from the profunda artery in this region, but Tonkoff (describing two to three branches) and Ramage (describing two to nine branches) alone gave details.

Certain features of the neurovascular arrangements in this region are worthy of comment. Ramage previously commented on the division of the profunda artery, in the majority of cases, into two vessels of almost equal size, called proximal and distal, which accompany the nerve on opposite sides as far as the lateral intermuscular septum. It is the proximal branch which accompanies the nerve through the lateral intermuscular septum. The presence of such an arrangement has been confirmed in this investigation. Ramage distinguished between the nutrient arteries arising from the proximal and those arising from the distal division, but no such distinction was drawn in this study. Again, it is common for many of the branches of the nerve to separate from the main trunk high in the groove but to accompany it for some distance before finally leaving to pass to their destination. Consequently, the radial nerve frequently has the appearance of a collection of loosely arranged strands or collaterals as it descends in the groove. The vascular pattern is modified accordingly. The nerve shows many superimposed vessels; one series is arranged along the principal trunk, while the other is disposed on each of its collateral branches. Bourguet reported a similar arrangement and is the only other investigator to do so. In the present series the number of nutrient branches given in the tables refers only to vessels passing to the principal trunk of the nerve.

Intermuscular Furrow.—In this region the nerve receives its supply by direct, and occasionally by indirect, nutrient arteries from the anastomosis between the profunda and the anterior radial recurrent artery.

Tonkoff mentioned only the source and gave no details. It is often difficult to establish the origin of some of the muscular branches in this region, but it is probable that some of them are originally derived, as Tonkoff stated, from the brachial artery. Bartholdy referred only to the supply from the profunda artery in this region.

Comment.—There is general unanimity concerning the vessels from which the nutrient arteries take origin, and all authors are agreed on the importance of the supply from the subscapular and profunda arteries. The large and constant supply in the spiral groove is a striking feature. In general the number of vessels observed in the present study exceeded the number reported by Ramage and Tonkoff.

Bartholdy claimed that the length of the nerve from its origin to the site of entrance of the first nutrient artery is often 8 to 10 cm. This obser-

vation was confirmed in the present study. Between its origin and its entrance to the spiral groove the nerve received fewer arteries than elsewhere along its course, and frequently this segment of the nerve was supplied solely by descending intraneural channels which reached it from the posterior portion of the cord.

As in the case of the median and ulnar nerves, the direct type of nutrient artery predominates. However, both Bartholdy and Ramage described a larger number of indirect nutrient arteries from the brachial artery than was observed in the present investigation.

As far as the spiral groove the fasciculi of the nerve are compactly arranged, and over this section the largest intraneural arterioles run on or just beneath the surface of the nerve; distal to this point, where the fasciculi are more loosely arranged, the arterioles are scattered irregularly among them.

SUPERFICIAL RADIAL NERVE

The blood supply of this nerve was examined from its origin to the point where it passes on to the dorsum of the forearm. The source and number of vessels reaching it are set out in table 4.

Bartholdy described a supply from the anterior radial recurrent artery and from the muscular and cutaneous branches of the radial artery. Tonkoff referred only to the radial supply, which is represented by four to five twigs from its muscular and cutaneous branches. According to him the nerve is rarely supplied directly from the main artery. Ramage listed a supply from the anterior radial recurrent artery (one to four branches) and from the radial artery (one to four direct and one to five indirect branches). The results of the present investigation were in general agreement with the observations of Ramage.

POSTERIOR INTEROSSEOUS NERVE

The nerve is accompanied by and supplied from the anterior radial recurrent and posterior interosseous arteries, the anastomosis between them in the supinator muscle and occasionally, in the distal part of the forearm, the termination of the anterior interosseous artery after that vessel has pierced the interosseous membrane. The source and number of arteriae nervorum are set out in table 4, and the figures are in general agreement with those given by Ramage. Both Bartholdy and Ramage described a supply from the vessels named, except for the anterior interosseous artery, but Ramage alone provided details of that supply.

TABLE 4.—*Blood Supply of the Superficial Radial and Posterior Interosseous Nerves*

	Superficial Radial Nerve				Posterior Interosseous Nerve					
	Anterior Radial Recurrent		Radial		Anterior Radial Recurrent		Anastomosis,	Posterior Interosseous		Anterior Interosseous
	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Direct	Indirect	
1 Left	—	1	2	3	—	—	—	3	—	1
Right	1	—	1	[illegible]	—	2	—	1	2	—
2 Left	—	—	2	1	1	—	—	2	—	—
Right	2	—	2	1	—	—	1	—	1	1
3 Left	2	—	1	1	1	—	—	1	—	—
Right	3		1	—	1	—	—	2	—	—
4 Left	2	—	3	1	—	—	1 Ind	—	1	1
Right	—	—	4	—	1	—	—	—	1	—
5 Left	—	—	4	2	—	1	—	1	2	1
Right	1	—	1	[illegible]	1	—	—	2	1	—
6 Left	—	—	1	1	1	—	—	2	—	1
Right	—	—	1	2	1	—	—	[illegible]	1	—
7 Left	1	—	—	2	—	—	1	1	1	—
Right	1	—	2	2	1	—	1	2	—	—
8 Left	—	—	—	1	1	—	—	2	—	—
Right	—	—	—	—	1	—	—	1	—	1
9	—	—	2	2	2	—	—	—	—	1
10	1	—	—	1	—	—	1	—	—	—
11	—	—	—	—	—	—	1	—	—	1
12	1	—	—	—	—	—	—	2	1	—
13	—	—	2	2	1	—	—	2	1	2
14	1	—	—	1	—	—	2	—	—	1
15	—	—	1	4	2	—	—	—	2	—
16	—	—	—	—	—	—	—	1	1	—
17	—	1	—	2	1	—	—	1	—	—
18	2	—	1	2	—	—	—	3	—	—
19	—	—	3	1	—	—	—	2	—	—
20	1	—	1	—	1	—	—	[illegible]	—	2
21	—	—	1	—	—	—	—	[illegible]	—	—
22	1	—	—	1	1	1	—	1	1	—
23	—	—	—	2	[illegible]	—	—	2	—	1
24	—	—	2	4	[illegible]	—	—	1	—	—
25	2	—	1	1	[illegible]	—	—	2	—	—
26	1	—	—	2	—	—	—	1	1	1
27	1	—	—	1	1	—	—	[illegible]	—	1
28	1	—	—	4	—	1	—	2	—	1
29	1	—	1	2	1	—	—	1	—	2

COMPARISON OF BLOOD SUPPLIES OF MEDIAN, ULNAR AND RADIAL NERVES

An important point to be decided is whether or not there is any significant difference in the blood supply not only of different nerves but of different segments of the same nerve. Before embarking on an investigation to settle this point, one must define exactly what is meant by the blood supply of a nerve. This has not been attempted, so far as I am aware, by any previous investigator. Many workers appear to have regarded the blood supply of a nerve as synonymous with the number of nutrient arteries it receives, but a study of the number of vessels alone can give no true conception of the blood supply of a nerve. Again, one frequently meets with such terms as "blood supply," "richness of blood supply," "richness of vascularization," "greater, better or richer blood supply" and "poorer blood supply," without any qualification to indicate whether the expression refers to the number, size and intraneural distribution of the arteriae nervorum or to the amount of blood reaching the part. "Blood supply" has an anatomic and the other terms a physiologic significance, and they differ in that, though the anatomic arrangement influences the amount of blood reaching the nerve, additional, and highly relevant, factors participate in controlling the supply. Consequently, anatomic studies alone, such as have been undertaken in this investigation, cannot furnish conclusive evidence concerning the actual amount of blood reaching the nerve, though they do provide an essential basis for studies of the latter. It is proposed in this paper to distinguish between the term "blood supply," which will be taken to have a purely anatomic basis, and such terms as "richness of supply," "richness of vascularization" and "better" or "poorer blood supply," which will be taken to have a physiologic implication. It is obvious, then, that on the basis of the observations recorded in this investigation one is justified in comparing, for the three nerves, only the anatomic, and not the physiologic, factors.

Even when employed in a strict anatomic sense, the term "blood supply" requires further elaboration, since it could refer, in turn, to the number or size of the arteriae nervorum, to the structural features of the intraneural pattern, to the supply to the entire nerve trunk, which incidentally involves more tissues than nerve fibers, or to the supply to individual nerve fibers contained in the trunk. For example, the sciatic nerve receives larger and more nutrient arteries than does the axillary nerve. From a consideration of this feature alone it might reasonably be concluded that the sciatic nerve receives a greater blood supply than the axillary nerve, though examination of the intraneural pattern and an analysis of the supply to individual nerve fibers would not necessarily lead to the same conclusion. It has been established that, for all the peripheral nerves examined, the supply to each nerve fiber, irrespective of the peripheral nerve which carries it or of its position in the nerve, is substantially the same. Consequently, in the present discussion the term "blood supply" will be restricted to the supply to the peripheral nerve trunk, and comparison of the supplies to the three nerves has been based on the size and number of the arteriae nervorum received by each nerve and the structure of the intraneural pattern.

It is now proposed to analyze, in the manner outlined, the supply in the 37 specimens examined, in an attempt to detect any significant differences in the blood supply of (1) the median, radial and ulnar nerves in the upper arm, (2) the median nerve in the arm and forearm, (3) the ulnar nerve in the arm and forearm, (4) the median and ulnar nerves in the forearm and (5) the superficial radial and posterior interosseous nerves.

Ramage [9] is, so far as I can ascertain, the only other investigator who has devoted any attention to this problem, but his observations were limited and the methods by which he arrived at his conclusions not always clearly stated. His paper, however, must be reviewed in some detail at this point, since his are the only data available for comparison with the observations made during this investigation. .

Ramage examined by the injection method the blood supply of the median, ulnar and radial nerves in 8 adult and 17 fetal arms. His procedure was to dissect and count, in each specimen, the vessels passing to each nerve in the upper arm and the forearm. From the data obtained he averaged the number of nutrient arteries to each individual nerve in both situations. He reported the numbers in the accompanying tabulation as the average per specimen,

	Nutrient Arteries	
Nerve	Arm	Forearm
Median	3.8	6.4
Ulnar	3.8	7.16
Radial	6.2	...

and from these figures he drew his conclusions.

1. The number of arteries passing to a nerve in the forearm exceeds that reaching the nerve in the upper arm. He stated, however, that the branches

are smaller in the forearm and asserted, without producing any further evidence, that "the blood supply is actually better in the upper arm than in the forearm."

2. The number of arteries to the musculospiral nerve exceeds the number to either the median or the ulnar nerve in the upper arm. He admitted that it is difficult to say on the basis of dissections whether or not the blood supply is greater but claimed that a microscopic examination of injected material indicated that it is so. Reference to his observations on the relative vascularity of the superficial radial and posterior interosseous nerves will be made in the section of the text devoted to this question.

Thus Ramage, in establishing his conclusions, worked solely on the basis of the average number of nutrient vessels received per nerve for the whole series. No attempt was made to compare, in each separate specimen, the number passing to each of the three nerves in the upper arm and in the forearm respectively. Such a procedure, and this is the one which has been adopted in this investigation, would have necessitated some modification of his conclusions.

Median, Ulnar and Radial Nerves in the Upper Arm.—The great irregularity in the number of arteriae nervorum is shown in table 5. The ranges of variation are similar for all three nerves, and this makes comparison of them extremely difficult. If, however, the numbers to the three nerves in the same specimen are compared, the following data are obtained:

No. of Nutrient Arteries	No. of Specimens
Radial and Ulnar Nerves	
Equal	9
Greater to the radial	16
Greater to the ulnar	12
Radial and Median Nerves	
Equal	5
Greater to the radial	19
Greater to the median	13
Ulnar and Median Nerves	
Equal	6
Greater to the ulnar	14
Greater to the median	17

Such an analysis admittedly neglects degrees of difference, but it appears to justify the following conclusions:

1. No nerve consistently receives more nutrient arteries than any other.

2. In only a small proportion of cases do nerves receive an equal number of nutrient arteries.

3. Any nerve may receive more nutrient arteries than its fellows.

4. In a small majority of the specimens the number of nutrient arteries to the radial nerve exceeds the number to the ulnar or median nerve, and the number to the median nerve exceeds that to the ulnar nerve. The number of specimens examined is too small, however, to give data of statistical value.

5. On the basis of numbers alone it is impossible to assign a constantly greater blood supply to any one nerve.

TABLE 5.—*Number of Nutrient Arteries Passing to Median, Ulnar, Radial, Superficial Radial and Posterior Interosseous Nerves*

	Median		Ulnar				
	Upper Part of Arm	Forearm	Upper Part of Arm	Forearm	Radial	Superior Radial	Posterior Interosseous
1 Left	5	2	5	12	6	6	4
Right	13	4	13	11	13	5	5
2 Left	8	7	10	19	10	3	3
Right	6	3	6	17	7	5	3
3 Left	6	3	4	8	6	4	2
Right	6	9	7	5	14	4	3
4 Left	8	3	7	9	7	6	3
Right	5	3	5	7	7	4	2
5 Left	5	1	6	5	9	6	5
Right	8	2	8	9	8	5	4
6 Left	8	1	7	9	11	2	4
Right	8	2	9	8	6	3	5
7 Left	5	3	3	4	8	3	3
Right	4	2	6	6	9	5	4
8 Left	4	5	7	7	7	1	3
Right	5	5	4	8	5	—	3
9	7	11	3	9	8	4	3
10	5	4	8	10	7	2	1
11	8	6	7	12	5	—	2
12	7	2	6	10	6	1	3
13	11	2	10	9	7	4	6
14	7	1	8	7	10	2	3
15	5	1	4	9	6	5	4
16	8	2	9	16	11	—	2
17	7	4	4	5	5	3	2
18	9	2	5	5	5	5	3
19	8	1	6	3	5	4	2
20	14	5	6	7	4	2	6
21	6	2	7	2	6	1	3
22	5	3	7	6	6	2	4
23	9	3	7	6	5	2	6
24	6	2	10	9	8	6	4
25	5	3	11	3	10	4	5
26	5	2	7	5	8	3	3
27	7	3	7	2	6	2	5
28	9	4	6	4	6	5	4
29	13	2	10	4	10	4	4

The size of the arteriae nervorum is subject to substantially the same variations in each nerve in the same specimen. Thus, the largest vessel to one nerve can be matched in size by an arteriole to another nerve. In this connection, however, the relation between size and number should not be neglected. From the study of size alone it is impossible to assign a greater blood supply to any one nerve.

The manner in which the intraneural vascular pattern is established is fundamentally the same in all three nerves, and the terminal capillary meshwork is of approximately the same density in all situations. Microdissection and histologic studies have, however, revealed variations in the detailed structure of this pattern in all three

nerves which are so inconstant and irregular that no two patterns are identical. Consequently, there is no pattern which is constant or characteristic for any one nerve, while the form it will take in a nerve, or in a segment of the nerve, is quite unpredictable. These variations appear to be determined by the number and size of the arteriae nervorum, by their site of entry and mode of branching within the nerve and by the fascicular pattern of the nerve and its connective tissue framework. All these morphologic features are known to be variable. The pattern is apparently designed to provide the most effective blood supply to the peripheral nerve in terms of its anatomic structure, and the variations observed are but a reflection of the measures adopted to achieve this. From a study of the intraneural vascular pattern in all three nerves, in the same and in different specimens, it may be concluded that though a comparison of the pattern of any two nerves will reveal obvious differences, there is nothing in these differences to suggest that one receives a better or a poorer blood supply than the other.

Thus, the number and size of the arteriae nervorum, together with their distribution within the nerve, are subject to such a wide range of variation, not only in the three nerves but in the same nerve in different specimens, that on the basis of anatomic observations alone it is impossible to reach any definite conclusion regarding the relative richness of supply to the various peripheral nerve trunks. The observations demonstrate that, with regard to the three anatomic features under discussion, there are inconstant and unpredictable differences in the three nerves and in the same nerve in different specimens. There is nothing to suggest from the evidence available that such differences can in any way be interpreted as an indication of a richer or a poorer blood supply. They appear to be due to variations designed to give, under prevailing anatomic conditions, the most effective blood supply to the peripheral nerves. It is conceivable, however, that these minor structural differences and variations imposed on the basic pattern may be a manifestation of much greater functional ones; but since they are common to all three nerves, there do not appear to be any grounds for attributing differences in the reaction of these nerves to injury, mechanical or otherwise, to any specific difference in the vascular pattern.

Median Nerve in the Upper Arm and Forearm.—The size and distribution of the median artery render difficult any comparison of the blood supply of the nerve in the upper arm and that of the nerve in the forearm. The number of nutrient arteries to the nerve in the upper arm exceeds in the great majority of cases (33 out of 37 specimens) the number to the nerve in the forearm (table 5). The number of arteriae nervorum appears to be closely related to their size and to the proximity of the parent vessel to the nerve. It is suggested that the median nerve receives fewer nutrient arteries in the forearm because there is no large limb artery accompanying the nerve in this region. As already observed, this is compensated for principally by the large size of the median artery or by long descending intraneural channels. Exclusive of this artery, however, the arteries reaching the nerve in the upper arm are usually, but not invariably, larger than the arteries reaching it in the forearm.

In general, the large intraneural arterioles in the upper arm are present on or toward the surface, whereas in the forearm they are, with the exception of the median artery, usually more centrally placed. Apart from this difference, which is by no means constant, the intraneural vascular pattern is subject to such a wide range of variations from one level to another and from one subject to another that there is no pattern which is constant or characteristic for any one part of the nerve. These local differences which are observed along the entire length of the nerve are but a reflection of the measures undertaken to assure, under the prevailing anatomic conditions, the most effective blood supply to the nerve.

There is nothing to suggest, from the anatomic evidence available, that one part of the nerve receives a better or a poorer blood supply than another.

Ulnar Nerve in the Upper Arm and Forearm.—The number of nutrient arteries to the nerve in the upper arm as compared with the number to the nerve in the forearm is as follows:

No. of Arteries	No. of Specimens
Equal	3
Greater in the forearm	18
Greater in the upper arm	16

Ramage claimed, however, that the number in the forearm always exceeds that in the upper arm.

In each specimen the largest nutrient arteries are usually, but not invariably, noted in the upper arm. When, however, the size and number are studied together in the same specimen, these two morphologic features are found to bear an inverse relation to one another. With regard to the structure of the intraneural vascular pattern along the length of the nerve, the observations were identical with those recorded for the median nerve, and the same conclusions apply.

On this evidence it is impossible to assign a constantly greater blood supply to any particular segment of the nerve.

Median and Ulnar Nerves in the Forearm.—The number of nutrient arteries to the two nerves in the forearm in each specimen is shown in table 5. In the majority of specimens (31 out of 37) the number of nutrient arteries to the ulnar nerve exceeded the number to the median nerve, the difference being explained in some measure by the disposition of the large arteries relative to the two nerves in the forearm.

The size and distribution of the median artery render difficult any comparison between the blood supply of these two nerves. There appear, however, to be significant differences in the number of nutrient arteries reaching the nerves in the forearm, though the smaller number to the median nerve is usually compensated for by the large size of the median artery. With the exception of this vessel there is no significant or constant difference in the size of the nutrient arteries passing to the two nerves.

A comparison of the intraneural pattern in the two nerves gave results identical with those previously described in the three preceding sections, and the same conclusions consequently apply.

Thus, it is impossible to assign a constantly greater blood supply to any particular segment of either nerve.

Superficial Radial and Posterior Interosseous Nerves.—Comparison of the number of arteries to each nerve as observed in this investigation with the figures listed by Ramage gave the following results:

	No. of Specimens	
No. of Nutrient Arteries	This Series	Ramage's Series
Equal to the two nerves	5	7
Greater to superficial radial nerve	17	13
Greater to posterior interosseous nerve	15	4

In the present investigation neither nerve consistently received more arteries than the other, and in only a small majority of specimens did the number of arteries passing to the superficial radial nerve exceed the number to the posterior interosseous nerve. Ramage's figures indicate a higher incidence for the superficial radial nerve, though, on the basis of his methods of comparison, he gave the average number of arteries per specimen as 4.05 and 4.6 to the posterior interosseous and the superficial radial nerves respectively. However, in comparison of the blood supply of these nerves he claimed to have demonstrated that "when sections of the posterior interosseous and radial nerves are compared, it is found that the area of nervous tissues in the two is about equal, but the area of the blood vessels in the radial is three and a half times as great as the area of the blood vessels in the posterior interosseous." I have been unable to confirm this observation. A comparison of the number, size and disposition of the arteriae nervorum failed to reveal any constant or characteristic differences for the two nerves. On the contrary, an analysis of the pattern suggests that, despite the variations, the blood supply to individual nerve fibers in the two nerves is substantially the same.

SUMMARY: GENERAL FEATURES

1. Each peripheral nerve is abundantly vascularized throughout its entire length by a succession of vessels which by their repeated division and anastomosis within the nerve outline an unbroken intraneural vascular net.

2. The arteriae nervorum arise at irregular intervals from the limb arteries or their branches which establish an intimate anatomic relationship with the peripheral nerve or which, at most, are not far distant from it.

3. The vessels which supply the nerve exclusively and which take origin from the main vessel, or from one of its named branches, are called direct nutrient arteries. Opposed to this type are the nutrient arteries which, because of their origin from branches (muscular or subcutaneous) destined to supply extraneural tissues predominantly, are referred to as indirect. The former type predominate in the case of the large peripheral nerves of the limbs.

4. For each individual nerve there is a reasonably constant group of arteries which, by the nature of their anatomic disposition, are favorably situated to supply the nerve and from which the arteriae nervorum are consequently derived.

5. Despite the presence of this reasonably constant vascular pathway, both the number and the precise site of origin of the arteriae nervorum arising from the vessels composing it vary over wide limits—not only from subject to subject but on the two sides of the body.

6. There are certain regions where nerves habitually receive arteries.

7. Despite the variability in the number and site of origin of the arteriae nervorum, their disposition may be such, particularly in certain regions, that it is impossible to free a nerve from the surrounding tissues for more than a few centimeters without sacrificing some of the vessels supplying it.

8. Extensive segments of a nerve which do not receive any nutrient arteries are frequently

seen. Microscopic examination of these segments fails to demonstrate any modification of the fundamental character of the intraneural vascular pattern, the segment being nourished and the pattern maintained by large descending intraneural vessels derived from the last entering nutrient artery.

9. The number and size of the arteriae nervorum are variable morphologic features. There appears to be an inverse relation between the two.

10. Larger nerves do not necessarily receive more vessels than smaller nerves.

11. The caliber of the nutrient arteries fluctuates over wide limits. The largest artery seen measured 1 mm. in diameter.

12. The largest vessels run to the largest nerves, though the largest nerves do not invariably receive larger arteries than do smaller nerves. The largest arteries in the upper limb are present in the upper arm.

13. Both size and number must be taken into account in estimating the relative vascularity of different segments of the same nerve and that of corresponding segments of different nerves.

14. The size and the length of the nutrient arteries are independent features. The length appears to be determined by the proximity of the parent vessel—the closer the parent artery. the shorter the nutrient branch.

15. The nutrient vessels take the most direct route to the nerve and are therefore straight or gently curved.

16. Nutrient arteries, on or adjacent to the nerve they are to supply, outline a variety of patterns of distribution.

17. On entering a nerve a nutrient artery may be distributed in one of several ways.

18. The intraneural pattern is composed of arterioles, precapillaries, capillaries and venules.

19. The largest intraneural arterioles are observed on the surface of the nerve and in the interfascicular tissues, where they branch to form a series of longitudinally disposed channels of arteriolar, precapillary and capillary type.

20. There is a general tendency for the largest vessels to be situated toward the center of the nerve in the forearm and at the periphery in the upper arm.

21. The largest intraneural arterioles in the arm are usually, but not invariably, seen in the upper arm.

22. From the interfascicular arterioles finer branches pass into the perineurium and fasciculi —precapillaries predominate in the former and capillaries in the latter. These branches are also longitudinally disposed.

23. The longitudinally directed epineurial, interfascicular, perineurial and intrafascicular vessels repeatedly give off side branches, more or less at right angles, in all directions at frequent but irregular intervals. These branchlets redivide in a similar manner and finally anastomose to give a fine terminal intraneural vascular net composed of rectangular meshes disposed in the plane of the longitudinal axis of the nerve.

24. The number, size and position of the interfascicular longitudinally directed vessels vary from level to level.

25. Though the intraneural vascular pattern has the same fundamental structure in all nerves, modifications which are determined by the number, size, position and manner of branching of the intraneural arterioles are superimposed on the basic structure. Nevertheless, the disposition of the terminal intrafascicular capillary meshwork is such that the number of capillaries per unit area of fibers appears to be relatively constant, irrespective of the nerve or their position in it. It may reasonably be inferred from this that the blood supply to the individual nerve fibers is, on anatomic grounds at least, substantially the same.

26. A characteristic feature of the intraneural pattern is the considerable overlap of supply which obtains between nutrient arteries entering at different levels. This, together with the profuse anastomosis, renders it unlikely that any vessel will dominate the intraneural circulation in any particular region or segment of the nerve. The vascular pattern has significance in connection with the production of local and general ischemia of the nerve.

27. Venules are the largest venous vessels seen in or leaving the nerve.

28. The structure of the intraneural venous pattern corresponds to the arterial arrangement. Venules and arterioles, however, do not always run together, either inside or outside the nerve, while counts suggest that the number of interfascicular venules exceeds the number of arterioles.

29. Veins may leave the nerve independently of the entering arterioles.

30. The number of veins leaving the nerve does not always correspond with the number of arteries entering it.

31. The emerging veins may terminate in the principal vein or veins accompanying the neighboring artery, in muscular veins or in the venous plexus in the wall of a neighboring artery.

SUMMARY OF THE BLOOD SUPPLY TO THE MEDIAN, ULNAR AND RADIAL NERVES

The results of a study of the source, site of origin, course and distribution of the nutrient vessels to the median, ulnar and radial nerves in 37 adult arms (tables 1, 2, 3 and 4) may be summarized as follows:

The principal blood supply to the median nerve in the upper arm comes from the axillary and brachial arteries. Arteriae nervorum are occasionally received from the ulnar collateral and supratrochlear arteries.

In the cubital fossa the nerve frequently receives nutrient vessels from one or several of the arteries which are related to it in this region, namely, the termination of the brachial artery and its radial and ulnar divisions and the common interosseous, anterior interosseous and anterior ulnar recurrent arteries.

In the forearm the nerve is supplied by the radial and ulnar arteries and by the median artery, which was present and provided the main supply in 27 specimens of the 37 examined.

The ulnar nerve is accompanied throughout its course by a continuous arterial chain, derived in turn from the axillary, brachial, ulnar collateral, supratrochlear, posterior ulnar recurrent and ulnar arteries. From this system the arteriae nervorum are derived. Occasionally the profunda brachii artery and a high radial artery establish a sufficiently intimate relation to the nerve to supply it. The principal and most constant supply is from the ulnar collateral and ulnar arteries.

The radial nerve is supplied by the axillary, subscapular brachial and profunda brachii arteries in the axilla and arm before entering the spiral groove; by the profunda brachii artery while running in the groove, and, finally, from the anastomosis between the profunda and the anterior radial recurrent artery in the intermuscular furrow between the brachialis muscle, medially, and the brachioradialis and the extensor carpi radialis longus muscle, laterally. The main supply in most cases is obtained from the profunda artery.

The superficial radial nerve is supplied by the anterior radial recurrent and radial arteries or their branches. The posterior interosseous nerve is supplied by the anterior radial recurrent and posterior interosseous arteries and from the anastomosis between them in the supinator muscle, and occasionally by the anterior interosseous artery in the distal third of the forearm.

The number, size, source, site of origin and site of entry into the nerve of the arteriae nervorum are inconstant in all three nerves. In no case was the arrangement bilaterally symmetric. The range of variation observed in these morphologic features was observed to correspond closely in all three nerves.

In an analysis of the blood supply of the median, ulnar and radial nerves with a view to the detection of differences, this supply was taken to mean the arteries to the entire peripheral nerve trunk, as opposed to the individual nerve fiber, and in this connection it was assessed in terms of the size, number and intraneural disposition of the arteriae nervorum. These features are, however, so irregular and the ranges of variation for all three nerves so similar as to render difficult any comparison of them on this basis. The observations, however, appear to justify the following conclusions:

1. In the upper arm, no nerve consistently receives more nutrient arteries than another.

2. In the upper arm any nerve may receive more nutrient arteries than its fellows.

3. In the upper arm the three nerves only occasionally receive the same number of nutrient arteries.

4. In the upper arm the number of nutrient arteries passing to the radial nerve exceeds in a small majority of cases that to either the median or the ulnar nerve, while in an even smaller majority the number to the median nerve exceeds that to the ulnar nerve. The number of specimens examined was too small, however, to give data of statistical value.

5. The size of the nutrient arteries varies over substantially the same limits for all three nerves in the upper arm.

6. Usually the number of arteries to the median nerve in the upper arm exceeds that to the median nerve in the forearm. The larger number in the upper arm appears to be compensated for in the forearm, in the majority of cases, by the large size of the median artery. Except for this vessel, however, the arteriae nervorum in the upper arm are usually, but not invariably, larger than the vessels in the forearm.

7. The number of arteriae nervorum to the ulnar nerve in the forearm exceeds, in a small majority of the cases, the number reaching it in the upper arm. Usually, but not invariably, the largest nutrient arteries are found in the upper arm. When the size and the number are studied together in the same specimen, an inverse relation is observed to obtain between the two.

8. With both the median and the ulnar nerve it is more common to see the largest intraneural arterioles situated on or toward the surface in the upper arm and occupying a more central position in the forearm.

9. The size and distribution of the median artery render difficult comparisons between the arteriae nervorum to the median nerve and those to the ulnar nerve in the forearm. However, there appears to be a significant difference in the number reaching the nerves in this situation, the smaller number to the median nerve being compensated for, in the majority of cases, by the large size of the median artery. Except for this vessel, there is no significant or constant difference in the size of the arteriae nervorum to the two nerves.

10. In a very small majority of cases the number of nutrient arteries to the superficial radial nerve exceeds the number to the posterior interosseous nerve. A comparison of the size and disposition of the arteriae nervorum passing to the two nerves fails to reveal any constant or characteristic difference.

11. The manner in which the intraneural vascular pattern is established is fundamentally the same in all three nerves, and the terminal capillary meshwork is, apart from minor variations, of approximately the same density in all situations. However, the size, number, position and mode of branching of the intraneural arterioles are subject to such a considerable range of variation in all nerves that no two patterns are alike in detail. There is certainly no pattern which is constant or characteristic for any one nerve or section of a nerve. Moreover, the form the pattern will take in any particular nerve is quite unpredictable. These variations appear to be of minor significance, and there is evidence to suggest that they are to a large extent determined by the number, size and site of entry into the nerve of the arteriae nervorum, by the fascicular pattern of the nerve and by its connective tissue framework. All these morphologic features are known to be variable.

Thus, so far as the intraneural pattern is concerned there are differences not only in the three nerves but in the same nerve in different specimens, as well as at different levels of the same nerve. These differences appear to be due to minor variations in the pattern designed to provide the most effective blood supply to the peripheral nerve in terms of its anatomic structure. However, though a comparison of the intraneural vascular pattern of two nerves reveals obvious differences, there is nothing in these differences to suggest that one nerve receives a better or a poorer blood supply than the other.

12. The observations demonstrate that with regard to the three anatomic features investigated (number, size and intraneural pattern) there are inconstant and unpredictable differences in the three nerves, in the same nerve in different specimens and in different segments of the same nerve. These differences appear to be due to variation designed to give, under the prevailing anatomic conditions, the most effective blood supply to the peripheral nerve. There is nothing to suggest from the evidence available that such differences can in any way be interpreted as an indication of a richer or a poorer blood supply. It is conceivable, however, that these local structural differences and variations imposed on the basic pattern in the three nerves are a manifestation of much greater functional differences, but since they are common to all three nerves, there appear to be no grounds for attributing differences in the reaction of peripheral nerves to injury, mechanical or otherwise, to any specific difference in the intraneural vascular pattern.

It must be admitted, however, that with establishment of the structural features of the blood supply the anatomic approach has reached the limit of its usefulness. Further inquiries concerning the functional significance of the pattern and its role in various physiologic and pathologic phenomena must be settled by further investigation, preferably of an experimental nature, and not by speculations based solely on the anatomic distribution of the vessels.

Mr. L. Preston and Mr. H. Marriott prepared the illustrations and the photomicrographs respectively which accompany this article.

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INTERPRETATION OF FINDINGS IN THE CEREBROSPINAL FLUID

I. THE DEMENTIA PARALYTICA * FORMULA AND THE NECESSITY OF ITS QUANTITATIVE DIFFERENTIATION

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DEFINITION

The term "dementia paralytica formula" will here be reserved for the humoral data alone as encountered in cases of typical, not effectively treated dementia paralytica, the acute forms being disregarded, while "dementia paralytica syndrome" is used for the ensemble of clinical and humoral data. With this restriction, the dementia paralytica formula is fairly uniform. It denotes a clear and colorless aspect of the cerebrospinal fluid and the following results of the obligatory tests.

1. In the quantitative analysis of the cell picture higher numbers of mononuclear cells are encountered with dementia paralytica than with other chronic forms of neurosyphilis, say 30 to 100 cells per cubic millimeter. Qualitatively, the peculiar polymorphism of the cells, which invariably include plasma cells, is so striking that previously it was believed to be specific.

2. The total protein content also is distinctly higher with dementia paralytica than with other chronic forms of neurosyphilis. While with cerebrospinal syphilis it hardly exceeds 60 mg. per hundred cubic centimeters, with dementia paralytica it ranges from 100 to 150 mg., infrequently exceeding 200 mg. per hundred cubic centimeters.

3. The titer of the blood in the complement fixation test for syphilis lies in the same maximal range as that in cases of early secondary syphilis before treatment.

4. The titer of the cerebrospinal fluid in the complement fixation test is distinctly higher with dementia paralytica than with other forms of neurosyphilis.

5. The colloidal gold test yields the so-called characteristic curve for dementia paralytica. The terms "dementia paralytica curve" (table 1, no. 4) and "syphilitic curve" (table 1, no. 2) do not mean that the curves are supposed to be "specific for" dementia paralytica and cerebrospinal syphilis respectively, but only that they almost invariably are "encountered" with these diseases.

The five tests mentioned are obligatory; an additional feature of the dementia paralytica formula is its resistance to change with routine treatment. The question whether this resistance may be taken for granted on the basis of a single examination or must be determined by tentative routine treatment and follow-up examinations was the main reason for the quantitative classification of those formulas which is subsequently suggested.

Finally, it may be mentioned that of the numerous additional tests, particularly permeability tests, suggested for the diagnostic examination of the cerebrospinal fluid in cases of dementia paralytica, none adds essential information to that furnished by the aforementioned five obligatory tests, provided optimal methods and correct interpretations are employed. Determination of the pressure and the Queckenstedt test are of no significance.

EXPERIMENTAL STUDY

METHODS

The cell examination consists of the study of a stained sediment and the cell count in a Fuchs-Rosenthal chamber, polychrome methylene blue without acetic acid being used. Only three cell forms are differentiated: red cells and mononuclear and polymorphonuclear leukocytes. For determination of the total protein content the micro-Kjeldahl method was used in the experiments. In routine work a turbidimetric method is employed, with use of sulfosalicylic acid and a photoelectric colorimeter. The technic is so controlled that it provides a practically satisfactory substitute for the micro-Kjeldahl method. The quantitative complement fixation test for syphilis of Wadsworth, Maltaner and Maltaner [1] and the quantitative colloidal gold test of Lange [2] are employed.

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* The term "dementia paralytica formula" has been used instead of the authors' "paretic formula" for conformity with the "Standard Nomenclature of Diseases" and with the policy of the American Medical Association Press.

1. Wadsworth, A.; Maltaner, F., and Maltaner, E.: Quantitative Studies of the Complement-Fixation Reaction with Syphilitic Serum and Tissue Extract: Technic of the Practical Quantitative Test, J. Immunol. **35**:217-234, 1938.

2. Lange, C.: Methods for the Examination of Spinal Fluid, Am. J. Syph., Gonor. & Ven. Dis. **23**: 638-668, 1939.

TABLE 1.—*Various Types, Quantitative Differences and Origin of Dementia Paralytica Curves*

Serial No.	Material	Mononuclear Cells, per 3 Cu. Mm.	Total Protein, Mg./100 Cc.	Complement Fixation Titer of Blood *	Complement Fixation Titer of Cerebrospinal Fluid	Colloidal Gold Reaction †													Type of Gold Curve
						Routine Serial Dilutions										Additional Dilutions			
						1:15	1:23	1:34	1:51	1:76	1:111	1:171	1:256	1:384	1:576	1:861	1:1,296	1:1,944	1:2,916
1	Normal cerebrospinal fluid.....	1	22	0	0	2.5	1	5	5.5 Maximum after 2 hr.	5.5 Maximum after 2 hr.	1	3.5	2.5	1	1	..	..	..	..	Normal ‡
2	Asymptomatic neurosyphilis....	11	51	55	6.3	7.5	8.5	10	12	13	11 Maximum after 2 hr.	12	8	7.5	5	..	..	..	..	Syphilitic
3	Tuberculous meningitis §.....	1,213	173	0	0	3.5	4.5	5	6	7	8.5	9.5	11 Maximum after 2 hr.	10	9	..	..	..	..	Hematogenous ‖
4	Clinically typical dementia paralytica	278	118	1,650	170	18	18	18	18	18	18	18	18 Speed maximum after 5 min.	18	18	18	18	18	16	True dementia paralytica type
5	Patient asymptomatic after routine treatment	26	47	153	19	18	18	18	18	18	18	18	11	8 5	6	..	..	..	..	Weak dementia paralytica type
6	Dementia paralytica formula after treatment	17	45	6.8	0	18	18	18	18	18	18	18	15	9.5	8	..	..	..	..	Weak dementia paralytica type
7	Clinically typical tabetic form of dementia paralytica	23	31	0	0	16	16	16	16	16	14	11	9	7.5	5	..	..	..	..	Residual dementia paralytica type
8	Dementia paralytica formula after fever therapy	1	26	7.5	2.3	12	12	12	11	9.5	9	7	5	1.5	3.5	..	..	..	..	Residual dementia paralytica type
9	Cerebrospinal fluid no. 4, after heating	..	..	..	..	6	6.5	7.5	9.5	15	17	18 Speed maximum after 5 min.	18	18	12					

		Different Serial Dilutions											
		1:1	1:1.5	1:2.3	1:3.4	1:5.1	1:8	1:11	1:17	1:26	1:38	1:58	1:86
10	Cerebrospinal fluid no. 4 in electrolyte-poor milieu	18 Speed maximum after 5 min.				18	15	13	11	10	9	7	5

* Titers obtained with quantitative complement fixation test.[1]

† The technic of the quantitative gold reaction was used.[2] The degrees of coagulation are determined with the gold color standard. The values range from 0; red, over violet to 10; blue, over blue-white to 20; colorless.

‡ The normal curve is characterized by maximum and strength.

§ Examination of the fluid revealed 123 polymorphonuclear leukocytes per 3 cu. mm., a cobweb-like coagulum of fibrin and tubercle bacilli.

‖ The hematogenous (meningitic) [?]) curve demonstrates passage of blood colloids into the cerebrospinal fluid, as encountered in cases of subarachnoid block and hemorrhage.

QUALITATIVE ASPECT OF THE DEMENTIA PARALYTICA FORMULA

Qualitatively, the dementia paralytica formula is characterized by the combination of a positive complement fixation reaction of the cerebrospinal fluid for syphilis and the colloidal gold curve for dementia paralytica. The grave prognostic significance of the dementia paralytica formula depends on the presence of the dementia paralytica curve, but only if technically "false dementia paralytica curves" are eliminated, which may be due either to an incorrect type definition or to an unsatisfactory p_H of the milieu.[3] On the basis of the reproducible results of the quantitative gold test, a "true dementia paralytica curve" (table 1, no. 4) is characterized by a broad plateau of complete coagulation, reaching a dilution of from 1:600 to 1:2,000. The coagulation becomes complete only after several hours, but after two hours, the usual reading time, it is almost complete. At this time the dementia paralytica curve is differentiated from all other types of curves by the absence of a prezone and a maximum. A misleading type definition is the widely adopted identification of "first zone curves" with dementia paralytica curves. It is easy to demonstrate experimentally that a true dementia paralytica curve is never a first zone curve and vice versa. In table 2, no. 4 is shown a true first zone curve, artificially elicited with a normal cerebrospinal fluid (table 1, no. 1) by bacterial contamination. Identification of this type with the dementia paralytica curve (table 1, no. 4) obviously destroys the practical value of the latter. Furthermore, in table 1, no. 8 is shown a "syphilitic first zone curve" as the residual of a dementia paralytica curve after treatment. The ensemble, particularly the almost normal total protein content, renders it obvious that prognostically this first zone curve has ceased to be a dementia paralytica curve. This quantitative definition of the dementia paralytica curve eliminates false curves due to incorrect definition.

Finally, that a true dementia paralytica curve is never a first zone curve is demonstrated by the "speed maximum," which lies in table 1, no. 4, in the dilution 1:256, and not in the first zone. The speed maximum is indicated by the dilution exhibiting the maximum speed of coagulation; in other types of neurosyphilis it is fairly identical with the maximum read after two hours. The speed maximum for the dementia paralytica curve disappears after about five minutes, because in a broad range of complete coagulation quantitative differences are bound to disappear finally. To sum up, the adequate utilization of the formula encountered with dementia paralytica requires a qualitatively and quantitatively correct definition of the dementia paralytica curve, as given here. To call a true dementia paralytica curve (table 1, no. 4) incorrectly a "first zone curve," as will be shown subsequently, is only a comparatively harmless misnomer. However, the identification of the true "first zone curve" (table 2, no. 4) with the dementia paralytica curves leads to serious trouble.

The second part of the qualitative aspect of the dementia paralytica formula concerns the question whether the difference between the curve for dementia paralytica and the curve for syphilis is only a difference of degree, as is almost generally believed, or one of kind. The experimental demonstration of the "dementia

TABLE 2.—*Telescoped and False Dementia Paralytica Curves*

Serial No.	Material	Technic	Various Serial Dilutions									Type of Curve
		Dilutions	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:500	1:1,000	
1	Dementia paralytica cerebrospinal fluid (table 1, no. 4)	Mastic [7]	4	5	5	5	5	5	4	2	1	0	Telescoped mastic curve 1/30 breadth of curve in table 1, no. 4
		Dilutions	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,500	1:5,000	
2	Dementia paralytica cerebrospinal fluid (table 1, no. 4)	Original colloidal gold test [6]	5*	5	5	5	5	5	4	3	1	0	Shorter gold curve, 1/6 of curve in table 1, no. 4
		Dilutions	1:15	1:23	1:34	1:51	1:76	1:114	1:171	1:256	1:384	1:576	
3	Tuberculous cerebrospinal fluid (table 1, no. 3)	Quantitative colloidal gold test, buffer p_H 6.2	18	18	18	18	18	17	17	17	16	15	False dementia paralytica, due to inadequate p_H
4	Normal cerebrospinal fluid (table 1, no. 1), after bacterial contamination	Quantitative colloidal gold test, correct p_H 7.4	5	5	5	4.5	4.5	4	3	2	1.5	1	Nonsyphilitic first zone curve

* In numbers 1 and 2 the degree of coagulation was subjectively appraised; 5 means complete coagulation. In numbers 3 and 4 the gold color standard was used.

3. Lange, C., and Harris, A. H.: The Significance of the p_H in the Gold Reaction, J. Lab. & Clin. Med. 29:970-975, 1944.

paralytica substance" shows that the peculiar character of the dementia paralytica curve is due to a radical qualitative difference.

After the cerebrospinal fluid in a case of dementia paralytica (table 1, no. 4) was heated for ten minutes at 70 C., the colloidal gold curve (table 1, no. 9) lost its dementia paralytica character and became more similar to the type obtained with tuberculous meningitis. This experiment suggests that heating inactivates a substance which is mainly responsible for the dementia paralytica character of the curve. This substance has not as yet been isolated, but it seems to be an abnormal pseudoglobulin-like compound, which is heat sensitive and nondialyzable; it is not removed with the euglobulins but is precipitated by 50 per cent saturation with ammonium sulfate. This substance is abnormal in that, contrary to the behavior of normal globulins in the cerebrospinal fluid, it coagulates colloidal gold in an electrolyte-poor milieu. Under these conditions, fortunately it can be demonstrated without any interference by other globulins. In order to maintain the same p_H as in the routine gold reaction, the cerebrospinal fluid in a case of dementia paralytica (table 1, no. 4) was dialyzed against a hundredth-molar solution of the usual phosphate buffer [2] of p_H 7.4. (Dialysis against distilled water would produce a p_H of about 5.7 to 6.0, with entirely different results.) The partially precipitated euglobulin after dialysis was removed and the supernatant fluid tested. A hundredth-molar buffer solution was used as diluent, and the acid "citrate gold" sol was neutralized to p_H 7.4 shortly before use. In this electrolyte-poor milieu, at p_H 7.4, in which neither normal globulins nor the heated cerebrospinal fluid of a patient with dementia paralytica has any effect on the colloidal gold solution, the curve shown in table 1, no. 10, was obtained. The curve exhibits a broad plateau of complete coagulation without a prezone. It must be taken into account that the strength of this reaction is considerably reduced by the low electrolyte concentration. As yet this reaction in an electrolyte-poor milieu at p_H 7.4 has been demonstrable only in cerebrospinal fluids yielding a curve of dementia paralytica type. The demonstration of the "dementia paralytica substance" provides the conclusive experimental differentiation of "chemically specific" and technically false dementia paralytica curves.

The gold reaction differentiates protein patterns which on the whole are etiologically nonspecific. In the dementia paralytica curve the nearest approach to etiologic specificity is reached, but still curves of this type are encountered in 1 and 2 per cent of cases of nonsyphilitic conditions. There remains, therefore, the establishment of its general pathogenic interpretation, i. e., the common causal factor that produces the dementia paralytica curve with etiologically different conditions. The hematogenous (meningitic) curve is encountered in cases of acute exudative inflammation, associated with polymorphonuclear cells, while the presence of fibrin demonstrates increased permeability. The "syphilitic curve," however, is encountered with chronic nonexudative inflammation, associated with mononuclear cells and normal permeability. Accordingly, the syphilitic curve seems to indicate chronic proliferative inflammation, as encountered with syphilis and multiple sclerosis, in contrast to bacterial infections. The dementia paralytica curve appears sporadically in association with advanced stages of epidemic encephalitis or other neurovirus infections and regularly with acute progressive stages of multiple sclerosis and with dementia paralytica, i. e., with forms in which extensive parenchymatous degeneration takes place. This is the reason that the designation "parenchymatous curve" [4] was suggested instead of "dementia paralytica curve," or the incorrect term "first zone curve." The term "dementia paralytica curve," according to the preceding unobjectionable definition, connotes "as encountered in cases of dementia paralytica." The term "parenchymatous curve" seems, at first, much better, since it is based on a sound pathogenic interpretation. However, the fact is not expressed that in cases of typical tabes, a parenchymatous form of neurosyphilis, a curve of this type is not encountered, a fact which accordingly indicates not simply parenchymatous degeneration, but "extensive parenchymatous degeneration as encountered with dementia paralytica." In short, some reference to dementia paralytica is hardly avoidable.

To sum up, the qualitative difference between the dementia paralytica and the syphilitic curve, or any other type, depends on the presence of an abnormal pseudoglobulin-like substance, indicating extensive parenchymatous degeneration and as yet detectable only by the colloidal gold reaction. These experimental facts explain the grave prognostic significance of the dementia paralytica curve, irrespective of the etiologic factor, which is to be determined on the basis of the syndrome as a whole.

QUANTITATIVE ASPECT OF THE DEMENTIA PARALYTICA FORMULA

In the quantitative aspect of the dementia paralytica formula, three parts must be considered: (1) the demonstration of syphilitic

4. Thompson, L. J.: Interpretation of the "Paretic Curve" in Lange's Colloidal Gold Test, Arch. Neurol. & Psychiat. **5**:131-145 (Feb.) 1921.

reagins, providing not only the etiologic diagnosis but, by the fixed or recurring reaction of the blood, a warning to examine the cerebrospinal fluid; (2) signs of degeneration, providing the prognostic differentiation of neurosyphilis, and (3) signs of inflammation, indicating the "activity of neurosyphilis and its amenability to specific treatment." After the specific diagnosis of neurosyphilis is established, the signs of degeneration and inflammation are of predominant significance. Before the consideration of details, it must be determined which parts of the dementia paralytica formula provide information about inflammation or degeneration and their quantitative degree.

The signs of degeneration, either clinical or humoral, determine the prognosis and the intensity of therapy, which varies in cases of neurosyphilis from routine therapy to the modern treatment of dementia paralytica. Clinical and humoral signs of degeneration are in most respects different and supplement each other. A dementia paralytica curve indicates that extensive degeneration is still going on, while in cases of a burnt-out process clinical signs of degeneration survive the active stage, i. e., the inflammatory process. Vascular insults may occur years after the primary inflammation has come to a standstill, as indicated by a normal cerebrospinal fluid. Tabetic signs of degeneration do not necessarily indicate "active neurosyphilis, amenable to treatment." Humoral signs provide no localization, while clinical degenerative signs may assume a specific character, through their topographic arrangement alone. With typical tabes no dementia paralytica curve is observed, in contrast to clinical signs and symptoms of parenchymatous degeneration or irritation. With tabes the clinical manifestation is more sensitive; the colloidal gold test is unable to detect such low degrees of degeneration. If extensive degeneration, as indicated by the dementia paralytica curve, takes place in "silent areas," no clinical manifestation can be expected. Humoral signs of degeneration may precede clinical manifestations by many years, a fact which obviously is significant from the standpoint of prevention. These considerable differences between clinical and humoral signs of degeneration are often overlooked.

The presumptive effect of therapy depends on the ratio of inflammation to degeneration, in which the degree of inflammation determines the "activity" of the process. It is well recognized that in cases of untreated dementia paralytica a low cell count, indicating torpid inflammation and an unsatisfactory defense mechanism, if associated with severe signs of degeneration, renders the prospect of therapy particularly unfavorable. In this connection two questions arise: (1) What signs of inflammation are available? and (2) Does the absence of such signs exclude "active neurosyphilis, amenable to specific treatment"?

First, the primary chronic inflammation in the central nervous system is inaccessible to clinical diagnosis as long as it is uncomplicated by parenchymatous irritation or degeneration. Only humoral signs are available. In cases of chronic neurosyphilis, the number of cells in the cerebrospinal fluid provides a quantitative expression of the inflammation in the meninges and the perivascular spaces because, under conditions of normal permeability, the pleocytosis must be of local origin.[5] Of the same significance is the increase in the total protein, which is caused by the lysis of the dead cells, shed into the cerebrospinal fluid. It will become clear subsequently why in the dementia paralytica formula an accurate determination of the total protein concentration provides the best standard for the degree of inflammation, of the "activity" of the process.

Secondly, it is controversial whether a normal cerebrospinal fluid excludes "active neurosyphilis." No agreement can be expected as long as the "syndrome of normality" is based on unsatisfactory or semiquantitative methods, and the presence of "activity" on possibly persistent clinical signs of degeneration (tabes). There is no evidence that "active neurosyphilis," connoting inflammation plus amenability to specific therapy, may persist anywhere in the central nervous system without eliciting demonstrable changes in the cerebrospinal fluid via the Virchow-Robin spaces, as with any hemorrhage. The alleged occurrence of a normal cerebrospinal fluid with "active neurosyphilis" seems to be based on the observation of the association of a normal cerebrospinal fluid with (persistent) clinical degenerative signs. That this apparent discrepancy between clinical signs of degeneration and a normal cerebrospinal fluid is never encountered in early stages of the infection suggests that it occurs only in cases of the burnt-out process. In short, the "syndrome of normality" (table 3, no. 4) renders the diagnosis of "active neurosyphilis, amenable to treatment," improbable, particularly in later stages of the infection.

With respect to the quantitative differences in dementia paralytica formulas, as yet only the changes encountered in cases of the typical, untreated disease have been considered, which are characterized by the strongest reactions given by

5. Lange, C.: Lumbalpunktion und Liquordiagnostik, in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1923, vol. 2, pp. 435-686.

any of the forms of neurosyphilis and by a rough parallelism of the various elements, which is one of the most distinctive features of the cerebrospinal fluid in this disease. Today, cases of the untreated disease are infrequent, and the available material consists predominantly of cases of dementia paralytica or questionable "predementia paralytica" in which more or less treatment has been received. In the course of treatment the aforementioned maximal strength and parallelism disappear, and three steps of "dissociation" may be observed (table 3). 1. The number of cells is reduced out of proportion to the remaining elements, except during exacerbations. 2. The complement fixation reaction of the cerebrospinal fluid occasionally may become negative at a time when the total protein concentration and the colloidal gold reaction are still distinctly abnormal, particularly in cases of the tabetic form of the disease. 3. In the last stage, when the colloidal gold curve approaches the normal, there may appear either a residual dementia paralytica curve (table 1, no. 8), suggesting residual degeneration without considerable inflammation, or a weak syphilitic curve, suggesting residual inflammation without extensive degeneration. Accordingly, a normal cell picture and a negative reaction to the complement fixation test are less valuable for the demonstration of cure than the total protein content, as the main indicator of inflammation, or the colloidal gold curve, as the main indicator of degeneration. The last two tests demonstrate quantitative differences throughout the whole range (table 3), from the strongest dementia paralytica formula down to "normality."

One may analyze now the results of the single tests in their quantitative relation to the three categories of information that the dementia paralytica formula provides: The first effect of therapy is a notable decrease in the number of cells, particularly when the dementia paralytica formula shows a maximal degree of pleocytosis. This cytolysis produces dissolved proteins and a fleeting increase in the total protein, the complement fixation titer and the colloidal gold reaction. Now, under conditions of (almost) normal permeability, the removal of this cytogenous protein is a far slower process than the cytolysis itself, as is well known from the study of hemorrhages.[5] This circumstance is of considerable technical significance; in cases of treated neurosyphilis the total protein concentration, being more persistent and accurately determinable, is far superior to the number of cells as an indicator of the inflammatory process, the "activity of the neurosyphilis." It is obvious that this situation requires a sufficiently accurate determination of the total protein concentration, for which the current qualitative or semiquantitative tests for globulin are unsatisfactory.

An optimal complement fixation test of the cerebrospinal fluid for syphilis is on the whole superior to most flocculation tests. However, even if the most sensitive complement fixation test is used, a negative reaction of the cerebrospinal fluid (table 1, no. 6) is of as little value as the cell picture in the demonstration of cure, which is to be based on the nonspecific total protein content and the colloidal gold reaction. In fact, for some purposes the complement fixation test of the blood is more important, the value however, depending largely on the method used. In the literature, from 10 to 19 per cent of negative reactions of the blood are reported in association with the "dementia paralytica formula" and from 30 to 48 per cent, in cases of neurosyphilis with a positive complement fixation reaction of the cerebrospinal fluid. The results of the quantitative complement fixation test [1] are strikingly different in this respect. Of cases of neurosyphilis in which a dementia paralytica formula was not exhibited but a positive complement fixation reaction of the cerebrospinal fluid was obtained, only 3 to 5 per cent yielded a negative reaction of the blood, even including cases of the later stages. In no case in which the dementia paralytica formula was obtained was the reaction of the blood negative, but here the elimination of a "false dementia paralytica curve" was probably more significant than the technical differences of the complement fixation test. Although the percentages previously cited are by no means conclusive, the fact that the quantitative complement fixation test [1] secures a considerably higher percentage of positive reactions of the blood in cases of neurosyphilis seems to be beyond doubt. This difference in the results of various technics usually is disregarded in the evaluation of methods, although it is most significant for the prevention of neurosyphilis. If, actually, optimal methods invariably secure a positive reaction of the blood in the presence of a dementia paralytica formula for the cerebrospinal fluid, all these cases of severe neurosyphilis could be detected by a routine examination of the blood, leading to examination of the cerebrospinal fluid and early administration of optimal therapy.

This technical factor is likewise important in the differentiation of the dementia paralytica formula from the "syndrome of multiple sclerosis," as encountered in acute progressive stages. The humoral part of the latter consists of negative complement fixation reactions of the blood and the cerebrospinal fluid for syphilis combined with a dementia paralytica curve; the latter invariably is a "weak dementia paralytica

curve," such as that indicated in table 1, no. 5 or 6. A similar humoral picture may be encountered with typical tabetic dementia paralytica (table 1, no. 7). It is obvious that the value of a negative, i. e., in any case, less conclusive, element in the formula largely depends on the previously analyzed ability of various methods to secure positive reactions of the blood in cases of neurosyphilis.

The colloidal gold reaction, as stated before, is too insensitive to detect the parenchymatous degeneration in cases of typical tabes. For this quantitative study it is necessary to select the most sensitive technic, of course, without its chemical specificity for the "dementia paralytica substance" being jeopardized. Since the dementia paralytica curve is characterized by a broad plateau of complete coagulation, the relative sensitivity of various "colloid reactions" may be roughly determined by the breadth of this plateau. The same dementia paralytica type of cerebrospinal fluid was first examined (table 1, no. 4) by the quantitative colloidal gold test.[2] The result of the original gold test,[6] in which "formol gold" was used, is shown in table 2, no. 2, and the result of an optimal mastic test,[7] in table 2, no. 1. The superior sensitivity of the quantitative colloidal gold test, due to the selection of an optimal "citrate gold" sol,[8] is manifest. The plateau with the "formol gold" test is one-sixth, and the plateau with the mastic test one-thirtieth, that for the quantitative colloidal gold test. The "telescoped" curves obtained with the mastic test indicate an absolute lack of sensitivity; a satisfactory prognostic differentiation of neurosyphilis cannot be based on the results of such a method, the even more unsatisfactory benzoin test being disregarded.

The chemical specificity of the dementia paralytica curve may today be controlled by the demonstration of the "dementia paralytica substance." "False dementia paralytica curves" are chiefly due either to the confusion with "first zone curves," already discussed, or to an unsatisfactory technic, particularly a too low p_H of the milieu. A comparison of table 1, no. 3, with table 2, no. 3, shows that a change in the p_H from 7.4 to 6.2 transforms a correct hematogenous (meningitic) curve into a false dementia paralytica curve.[3] Every modification of the colloidal gold reaction which uses acid colloidal gold solution without neutralization, or tries to compensate for lack of sensitivity by the addition of acid, is bound to yield "false dementia paralytica curves." In the quantitative colloidal gold reaction, the sensitivity is secured by the selection of an optimal colloidal gold solution,[8] and the specificity, by maintaining the obligatory p_H of 7.4 by use of a strong buffer as a diluent; the reproducibility is controlled by the use of an adequate test fluid. All these factors are made possible only by the use of a gold color standard. Tables 1 and 3 show that the results of the quantitative gold test run fairly parallel with the total protein concentration throughout the quantitatively different types of the dementia paralytica formula.

TABLE 3.—*Quantitative Classification of Dementia Paralytica Formulas*

	Types	Percentage in This Study	Total Protein, Mg. per 100 Cc.	Colloidal Gold Reaction	Complement Fixation Reaction of Blood	Complement Fixation Reaction of Cerebrospinal Fluid	Cell Picture
1	True dementia paralytica formula	32	About 100-150	True dementia paralytica curve (table 1, no. 4), complete coagulation up to dilutions of 1:600 to 1:2,000	Invariably strongly positive	Strongly positive, weaker than blood titer	In cases of untreated disease strong mononucleosis with polymorphism
2	Weak dementia paralytica formula	42	50-100	Complete coagulation up to dilutions of less than 1:500 (table 1, nos. 5 and 6)	Strongly positive	Sporadically negative (table 1, no. 6)	After treatment of little value, except in exacerbations
3	Residual dementia paralytica formula	26	25-50	Short plateau of incomplete coagulation (table 1, nos. 7 and 8) or atypical forms	Sporadically negative, before reaction of cerebrospinal fluid became normal	Often weakly positive, even if total protein content almost normal	After treatment of little value, except in exacerbations
4	Normal formula	..	15-25	Normal curve (table 1, no. 1)	Negative	Negative	0 2 mononuclears per 3 cu. mm.

QUANTITATIVELY DIFFERENT TYPES OF THE DEMENTIA PARALYTICA FORMULA

After the preceding technical and theoretic analysis, table 3 is self explanatory. The neces-

6. Lange, C.: Die Ausflockung kolloidalen Goldes durch Zerebrospinalflüssigkeit bei luetischen Affektionen des Zentralnervensystems, Ztschr. f. Chemotherap. **1**: 44-78, 1912.

7. Emanuel, G., and Rosenfeld, H.: Die Emanuelsche Mastixreaction der Rückenmarksflüssigkeit in neuer Form, Klin. Wchnschr. **6**:1375-1378, 1927.

8. Lange, C., and Harris, A. H.: A Citrate Gold of Optimal and Reproducible Sensitivity for Use in the Colloidal Gold Reaction: Its Preparation and Control, Am. J. Pub. Health **34**:1087-1092, 1944.

sity of differentiating these types of the dementia paralytica formula is as obvious as the fact that their differentiation requires optimal quantitative methods. Type 1 is well defined as the maximal and fairly uniform strength encountered with dementia paralytica; type 3 is as well defined by an "almost normal" total protein content. The lines of demarcation of type 2 are of necessity arbitrary. The percentages, calculated for the various types, are not assumed to be accurate, in view of the fact that the lines of demarcation of the types are not well defined and that inadequate data frequently accompany specimens. However, they seem to be sufficiently accurate to point out that only about one third of the dementia paralytica formulas, when they are detected and are to be evaluated for therapeutic considerations, are "true dementia paralytica formulas, as encountered with dementia paralytica."

COMMENT

Contrary to the predominantly qualitative concept of the dementia paralytica formula, Stokes [9] takes account of the strength of the curve for the disease in the ensemble of the dementia paralytica formula, which he calls the "red flag" of the disease. He states that fluids "in which the first-zone gold sol reaction is of great intensity, are almost invariably paretic." [9a] From his data, it is obvious that he means a true dementia paralytica curve, according to the previous definition. In addition, he states: [9b]

> Notwithstanding this necessity for cautious interpretation, the first-zone colloidal test in its presence or absence is the one most important single prognostic item in the spinal fluid examination with respect to syphilis.

In determination of the protein, Stokes still uses a qualitative test for globulin but points out that an accurate determination of the total protein might be preferable, which, indeed, in the preceding analysis was found to be the optimal standard for the quantitative differentiation of formulas of the dementia paralytica type.

Moore,[10] using an obviously different colloidal test and no quantitative specification, drew the following conclusion, to some degree different:

> The paretic formula . . . especially if treatment efforts fail to effect significant improvement, is of serious prognostic import. It indicates definitely that the patient is in danger of developing further neurologic progress which is particularly likely to be tabetic or paretic in nature.

The experience of one of us (C. L.) agrees in principle with that of Stokes. Only, while Stokes bases the quantitative specification of the dementia paralytica formula on more general terms, we wish to stress the necessity of basing the quantitative differentiation on optimal quantitative methods, yielding reproducible results, particularly in the determination of the total protein and the colloidal gold reaction. The controversial question whether the dementia paralytica formula, or, rather, the "true dementia paralytica formula," indicates dementia paralytica or, in early asymptomatic stages, "potential dementia paralytica," can, for obvious reasons, never be conclusively solved. From a practical standpoint, however, the question may be considered academic. The immediate problem, after a dementia paralytica formula indicating extensive parenchymatous degeneration is detected, concerns the selection of the adequate intensity of therapy in order to stop further progress of the disease, irrespective of whether or not it is assumed that the condition is dementia paralytica.

This practical task being considered, the question arises, as mentioned in the introduction, whether in the presence of a dementia paralytica formula the resistance to less intense treatment can be predicted from a single examination. Stokes's answer was: "No time for 'neo' now. Tryparsamide? Fever?" [9a] But this situation actually refers to a quantitatively defined formula for dementia paralytica. If Moore seems to be therapeutically more conservative, it must be considered that he speaks of a dementia paralytica formula generally without quantitative specification. The importance of wasting no time or money on presumably inadequate treatment after a dementia paralytica formula has been demonstrated can hardly be overrated. On the other hand, it seems beyond doubt that the selection of adequate therapy must take into account the striking quantitative differences of dementia paralytica formulas.

Without formulation of any detailed conclusions, it may be of value to attempt to elucidate the therapeutic situation by a few representative cases selected from earlier or asymptomatic stages.

CASE 1.—The cerebrospinal fluid was first examined fifteen months after infection, and after eight months of routine treatment had failed to yield a negative reaction of the blood. A "true dementia paralytica formula" was found, as indicated quantitatively by the total protein content of 132 mg. per hundred cubic centimeters, while the other results were in the same maximal range. In this case, the dementia paralytica formula was complete in that it included even the demonstration of resistance to routine treatment, so that the therapeutic decision was the simplest possible.

9. Stokes, J. H.: Modern Clinical Syphilology, ed. 3, Philadelphia, W. B. Saunders Company, 1944, (*a*) p. 119; (*b*) p. 116.

10. Moore, J. E.: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 368.

CASE 2.—A routine premarital blood test yielded a positive reaction for syphilis of a very high titer. The cerebrospinal fluid exhibited the strongest dementia paralytica formula, i. e., a total protein content of 178 mg. per hundred cubic centimeters. The question is whether it is at all sensible to try routine treatment under these conditions.

CASE 3.—Data such as are presented in table 1, no. 5, deserve most attention because of their frequency. With the use of a satisfactory method of determination of the total protein and the colloidal gold test, there cannot be the slightest doubt that although the formula is qualitatively of dementia paralytica type, it is not a dementia paralytica formula "as encountered with dementia paralytica," in contrast to the formulas in cases 1 and 2. The majority of the weak dementia paralytica formulas encountered in our experience are detected when the cerebrospinal fluid is submitted "for control of treatment," which generally means routine treatment. The main difficulty in cases of this type is to determine whether the inferior strength of the formula is the effect of routine treatment, so that a factor in the dementia paralytica formula, particularly essential for therapeutic considerations, is lacking, namely, the resistance to routine treatment. In an individual case, only follow-up study can determine whether the strength of the formula is progressive or regressive. In later stages of the infection regression seems to be the rule, so that the "weak dementia paralytica formula" does not seem to be the true formula with regard to the factor of greatest practical importance, namely, the resistance to treatment. In short, the weak dementia paralytica formula, constituting the largest number of formulas for this disease obtained in this laboratory, is distinctly different from the true dementia paralytica formula, "as encountered with dementia paralytica."

CASE 4.—The "residual dementia paralytica formulas" (table 1, no. 8) demonstrate beyond doubt that the qualitative concept of the dementia paralytica formula is unsatisfactory, since it includes without differentiation the strongest pathologic changes and almost normal quantitative factors.

To sum up, if a dementia paralytica formula is detected, particularly in a case of asymptomatic neurosyphilis, the main task consists in immediate selection of the most adequate form of therapy. For this decision, a consideration of the quantitatively different types of the dementia paralytica formula is indispensable.

SUMMARY AND CONCLUSIONS

The formula as encountered in cases of typical untreated dementia paralytica is one of the most distinctive and important diagnostic findings concerned with the cerebrospinal fluid. It provides the main prognostic differentiation of neurosyphilis, possibly in early asymptomatic stages. Qualitatively, it is characterized by the combination of a positive reaction for syphilis and a dementia paralytica (parenchymatous) colloidal gold curve and, quantitatively, by a strength of all reactions which is unrivaled by other forms of neurosyphilis. From the practical standpoint, its varying resistance to specific therapy is most significant.

A correct evaluation of the dementia paralytica formula requires the elimination of "false dementia paralytica curves," due either to confusion with first zone curves or to an unsatisfactory p_H of the milieu. The qualitative differentiation of the dementia paralytica curve from all other types of curves is based on the presence of an abnormal pseudoglobulin-like "dementia paralytica substance," indicating extensive parenchymatous degeneration. This explains the grave prognostic significance of any dementia paralytica curve, irrespective of whether it is encountered as an element of the dementia paralytica formula or as part of the "syndrome of multiple sclerosis."

When quantitatively standardized methods are used, particularly in the determination of total protein and in the colloidal gold test, striking quantitative differences in dementia paralytica formulas are demonstrable. Of cerebrospinal fluids that were submitted for control of treatment, only about one third yielded "true dementia paralytica formulas, as encountered with dementia paralytica," and two thirds were notably weaker. Whether a true dementia paralytica formula, detected in the early asymptomatic stage, means prospective development of the disease cannot be determined; besides, the question is comparatively irrelevant. At the moment of the detection, the problem of the presumptive resistance to antisyphilitic treatment is paramount, since it determines the selection of adequately intense therapy. The direct determination of this resistance by follow-up examinations may involve a waste of time and money.

Without premature conclusions, the results of quantitative methods suggest that the resistance to antisyphilitic treatment roughly parallels the strength of the dementia paralytica formula, which is best expressed by the total protein concentration. It is suggested that the current qualitative concept of the dementia paralytica formula be abandoned and that the connection between this formula and its varying resistance to therapy on the basis of quantitatively different types be studied.

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PREFRONTAL LOBOTOMY IN TREATMENT OF CHRONIC PSYCHOSES

WITH SPECIAL REFERENCE TO SECTION OF THE ORBITAL AREAS ONLY

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For the past decade the surgical approach to the treatment of mental disease has been attaining increasing prominence [1] and recognition [2] in this country. As an attack on the intact brain tissue for the relief of mental symptoms, it is comparable to differential section of the posterior trigeminal root for the relief of intractable physical pain.[3] The first, and isolated, attempts at surgical treatment of mental derangements can be traced back to Burckhardt's [4] unilateral multiple cortical excisions (1890), to Puusepp's [5] unilateral subcortical section of the centrum semiovale in the frontal region of the dominant hemisphere (1906 to 1910) and to Ody's [6] unilateral lobectomy (1936).

The recent discoveries in the field of neurophysiology [7] and psychopathology [8] were put into use by Egas Moniz and Almeida Lima [9] (1935) on the European continent. Freeman and Watts,[10] in this country, have introduced and improved the method of bilateral prefrontal coring by the substitution of bilateral subcortical transection of the four prefrontal quadrants in the plane of the coronal suture (bilateral prefrontal lobotomy).

Clinical reports [11] and suggestions [12] in the literature indicate that effective therapeutic results might be obtained by limiting the transection of the prefrontal lobe to the orbital areas alone. Such a procedure, if effective, would restrict the extent of destruction, as well as the postoperative sequelae and defects. We therefore decided to limit our operation to section only of the orbital region, or lower quadrants of the frontal lobe. The results obtained from this modified procedure form the basis of the present report.

METHOD

The surgical procedure was carried out with the patient under anesthesia induced with solution of tribromoethanol U. S. P. After preparation of the operative field, a point 3 cm. posterior to the lateral rim of the orbit and 5 cm. above the zygomatic process was marked out with methylrosaniline chloride.[10] A vertical incision of about 2 cm. was then made in the plane of the coronal suture and carried down to the bone. A perforator burr hole was made in the bone through the suture line at the point indicated, and the dura was opened in a cruciate fashion. After the surface of the cortex had been coagulated, a ventricle needle was introduced through a stab incision in the avascularized area in a direction at right angles to the sagittal plane in order to locate the tip of the ventricle. Occasionally additional bone had to be rongeured away anteriorly in order to reach the tip of the anterior horn. A Sachs dural dissector was introduced along the needle in front of the ventricle to a distance of 5 cm. from the surface of the skull. A cut was made in the plane of the coronal suture, the incision beginning at the level of the burr hole and being

A preliminary account of this investigation was read at a meeting of the St. Louis Society of Psychiatry and Neurology in January 1944.

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10. Freeman, W., and Watts, J.: Psychosurgery, Springfield, Ill., Charles C Thomas, Publisher, 1942.
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directed downward. The area above the burr hole was left intact. After the section a catheter was introduced, and irrigation with warm saline solution was carried out until the return was clear. In a few instances iodized poppyseed oil was injected to demarcate the plane of the section (figure). Closure was made in layers with silk. A similar procedure was carried out on the opposite side. The patients were routinely restrained for three days to prevent their pulling at the dressing.

CLINICAL MATERIAL

In this series, 45 patients at the City Sanitarium have been operated on since May 1942. Thirty patients of this series were studied for over twelve months after operation. In the latter group, the first 8 patients had the unmodified operation described by Freeman and Watts, and the next 22 patients had the modified operation, as here described.

These 30 patients had been mentally ill from one to twenty-seven years, the average duration being ten years, and had been institutionalized from one to twelve years, with an average period of three and one-half years. Many of these pateints showed not only social maladjustment but antisocial behavior on a noisy, combative and destructive level. The majority (85 per cent) had received various forms of shock therapy (insulin, metrazol, electric shock and nitrous inhalation), the average number of treatments being thirty-one (table 1) with no, or only transient, amelioration of symptoms. In general, the outlook for these patients as to remission or recovery was poor, and any postoperative change which occurred could be regarded as the result of the operation. The indications for operation were the chronicity and malignancy of the mental processes, the pronounced antisocial behavior, the suicidal tendencies and the failure to respond to any of the known treatments.

RESULTS

The distribution of and results for patients subjected to prefrontal lobotomy are outlined in table 2 and arranged according to psychiatric diagnosis and surgical method used. Three patients had affective reaction types; 1 patient, an obsessive-compulsive state; 2 patients, neurasthenia; 4 patients, epilepsy with psychosis, and 20 patients, that is, 66 per cent, schizophrenia.

TABLE 1.—*Data on Unsuccessful Preoperative Shock Treatment of Patients Who Underwent Section of the Orbital Area*

Disease	No. of Patients Treated	Insulin: No. of Patients Treated	Insulin: Average No. of Treatments	Metrazol or Electric Shock Treatment: No. of Patients Treated	Metrazol or Electric Shock Treatment: Average No. of Treatments	Insulin and Metrazol or Electric Shock Treatment: No. of Patients Treated	Insulin and Metrazol or Electric Shock Treatment: Average No. of Treatments	Totals: No. of Patients Treated	Totals: Average No. of Treatments
Affective reaction types	3	. . . .	..	3 (100%)	12	.....	..	3 (100%)	12
Obsessive tension states	1	. . . .	.	1 (100%)	7	.....	..	1 (100%)	7
Schizophrenias	20	3 (14%)	62	14 (70%)	28	1 (5%)	175†	16 (80%)	56
Psychoneuroses	2	1 (50%)	26	2 (100%)	13	1 (50%)	36	2 (100%)	19
Total	26*	4 (15%)	53	20 (80%)	23	2 (7.5%)	62	22 (85%)	31

* The data on 4 epileptic patients with psychosis are not included in the computation.
† Included with this figure are 60 nitrogen inhalation treatments.

Anteroposterior roentgenogram of a patient with catatonia after bilateral section of the orbital quadrants, showing distribution of the iodized poppyseed oil in the area of the section. The patient had been ill three and a half years and was now "much improved."

We considered the condition as "much improved" when the patient was able to resume his social activities and to return to his former level of occupation, as "improved" when the patient made a definitely better institutional adjustment and was assigned responsibilities which he had been incapable of assuming before the operation, as "slightly improved" when the patient's conduct and changes in behavior were such that nursing and custodial care were reduced and transfer to quieter halls and to a pleasanter environment was facilitated and as "not improved," when the patient showed no change in his behavior.

Two of the 3 patients with affective reaction types showed much improvement and were discharged. Both had depression with agitation. The condition of the third, with a chronic manic state, improved, and she was returned to her family.

One patient with obsessive-compulsive neurosis had a typical history dating from childhood,

with increasing symptoms during the years prior to institutionalization. After operation the compulsive activities gradually subsided. The patient was able to take a war job, in addition to the responsibilities in her home, and divorce proceedings instituted prior to her hospitalization were dropped by her husband.

Two neurasthenic patients, with several admissions to the institution, could not adjust on the outside before the operation. Their numerous somatic complaints progressively decreased after the operation. A somatic delusion which altered one patient's body image also disappeared. The other patient was discharged, became pregnant and is adjusting normally to the pregnancy, though she had formerly dreaded this possibility.

Four patients suffering from epilepsy with psychosis displayed sullenness, irritability, noisiness and violence as their common features. One patient responded to disturbing auditory hallucinations of an immoral nature with violent attacks on the environment. Her hallucinations subsided after the operation, but her seizures continued at about the same frequency. Her tendency to blame others for her difficulties is still present to some extent but does not now interfere with her adjustment on the outside as a housemaid. The other 3 patients have shown improvement and are now helpful and cooperative in the ward; however, shortly before the onset of their menses and of their epileptic seizures, they go through periods of increased irritability, the degree of which is less intense than before.

The schizophrenic group, table 3, comprised 2 patients with hebephrenia, 4 with catatonia and 14 (i. e., 70 per cent) with paranoia. Seven patients (30 per cent) showed much improvement; 4 improvement, and 9, slight or no improvement. The rate of recovery increases progressively from the hebephrenic to the catatonic to the paranoid group. The hebephrenic patient becomes more extroverted, interested and active; the catatonic patient loses his impulsiveness and negativism; the paranoid patient loses his intense interest in his delusions; he may or may not lose his hallucinations, but he certainly does not respond to them with the emotional impetus evident before operation. He does not answer the voices, does not fight back, does not try to keep the voices out by sticking his fingers in his ears. The outlook for the paranoid patients in general appears much more favorable than was anticipated.

One patient, with catatonia, failed to show improvement with the modified operation. After a four month period of observation, a second operation was performed, and all four quadrants were transected. This patient still shows no im-

TABLE 2.—*Results of Bilateral Prefrontal Lobotomy*

	Subcortical Transection of Lower Quadrants					Subcortical Transection of Upper and Lower Quadrants					
Disease	No. of Patients	Patients Much Improved	Patients Improved	Patients Slightly Improved	Patients Not Improved	No. of Patients	Patients Much Improved	Patients Improved	Patients Slightly Improved	Patients Not Improved	Total No. of Patients
Affective reaction types	3	2	1	..	..	..	..	..	..	..	3
Obsessive tension states	1	1	..	..	..	..	..	..	..	..	1
Psychoneuroses	1	1	..	..	..	1	1	..	..	..	2
Epilepsy with psychosis	2	1	..	1	..	2	..	..	2	..	4
Schizophrenias	15	6	4	3	2*	5	1	1	3	..	20
Total	22	11	5	4	2	8	2	1	5	..	30

* One patient had both types of operation.

TABLE 3.—*Results of Bilateral Prefrontal Lobotomy in Patients with Schizophrenia*

	Subcortical Transection of Lower Quadrants					Subcortical Transection of Upper and Lower Quadrants					
Type of Schizophrenia	No. of Patients	Patients Much Improved	Patients Improved	Patients Slightly Improved	Patients Not Improved	No. of Patients	Patients Much Improved	Patients Improved	Patients Slightly Improved	Patients Not Improved	Total No. of Patients
Hebephrenic	2	..	1	1	..	..	..	..	..	..	2
Catatonic	3	..	2	..	1*	1	1	..	..	..	4
Paranoid	8	4	1	2	1	3	..	..	3	..	11
Paranoid states	2	2	..	..	..	1	..	1	..	..	3
Total	15	6	4	3	2	5	1	1	3	..	20

* This patient had both types of operation.

provement, eight months after the second operation.

None of the patients became worse after the operation. No death occurred in our series either after operation or at a more remote period. There were no instances of infection. So far, in none of the patients has epilepsy developed. This sequela occurs, we believe, when the attack on the prefronal lobes is carried out through openings placed close to the premotor area; the resulting trauma, hemorrhage and edema which occur may more readily involve the motor regions and thus lead to the development of epileptic seizures. Our epileptic patients with psychosis exhibited no amelioration and no increase of the epileptic seizures after the lobotomy. Occasional transitory fluctuations in the blood pressure in either direction were noticed during the procedure, but no positive or permanent changes occurred.

Considerable thickening of the dura was a rather consistent observation for the patients with long-standing psychoses. In many patients a considerable collection of subarachnoid fluid was encountered and had to be evacuated. In some patients roentgenograms showed the injected iodized poppyseed oil intraventricularly; whether the negative pressure exerted by the suction caused a tear in the ventricle, or whether actual transection of the tip of the ventricle had taken place, is uncertain. Transection of the tip of the lateral ventricle in no way affected the therapeutic results.

Transitory incontinence occurred in 4 of the 22 patients in whom only the lower quadrants were sectioned and in 4 of 8 patients in whom all quadrants were transected. One patient had a dilated pupil on one side, which persisted for several days. Two patients had slight hemiparesis, which was minimal and rapidly disappeared. With 2 patients there was no speech production for about one week. Speech production was occasionally scanty and often in whispers, but it returned to its normal amount and intonation within a week. Some patients, however, exhibited transient slowing of speech, thought and motor activity; lack of interest, initiative and spontaneity, and flattening of facial expression. The retardation slowly disappeared, and the patient became more normal. These signs were less pronounced and returned to normal in a shorter period in patients in whom only the orbital quadrants were cut.

Delusional ideas might disappear rapidly or might continue with less emotional impetus than before. Auditory hallucinations might persist for some time but failed to keep the patient absorbed or upset. Postoperative confusion and disorientation were infrequently observed in patients, either with or without a favorable outcome. None of the patients was aware, or was willing to admit, that they had undergone an operation and showed no concern about it. Alertness and responsiveness on the first postoperative day did not interfere with the successful outcome of the operation. Improvement occurred gradually, within a few weeks, or might take as long as a year. Patience on the part of the physician was usually rewarded.

Most of the patients ate their meals heartily, some to excess. The gain in weight of the patients is indicated in table 4, and the results support the observations of Lyerly [13] and others. Frequently we noted an increase in tissue turgor and a fulness of facial features that made the patient appear younger.

During the period of convalescence the patient's psychotic behavior persisted to some extent; then inertia became more prominent, and the patient frequently complained of inability to overcome his dulness. The period of relative list-

TABLE 4.—*Correlation of Changes in Weight with Clinical Results of Bilateral Prefrontal Lobotomy*

Clinical Change	Section of Orbital Areas	
	Gain in Weight	Loss of Weight
Much improvement	22	
Improvement	6	
Slight improvement	3	
No improvement	..	1

lessness was followed by one of overactivity. It is at this time that the patient is most in need of assistance and direction toward a more normal adjustment. With anxiety diminished and the expression of the inherent trend reduced, a better integration of the personality can be established.

Study of the postparole status (table 5) reveals that at the time of writing 9 patients are keeping house and carrying the full burden of their responsibilities, 1 patient is partially employed, 3 patients are regularly employed, with 1 contributing to the manpower of the war, and another holds a position for the first time in her life. The operation apparently succeeds in salvaging considerable prepsychotic material which would have been irretrievably lost. The patients show resourcefulness, common sense, interest and planning for the future. Their lives are raised from an unsatisfactory level to one of useful activities. Their pathologic personality trends are now only faintly recognizable. The personality trends and the dynamics in the postoperative behavior are being carefully studied

13. Lyerly, J. G.: Prefrontal Lobotomy in Involutional Melancholia, J. Florida M. A. **25**:225, 1938.

and will be the basis of a future report, together with correlative psychologic testings.

COMMENT

The postoperative rate of recovery of 40 per cent of the total number of our patients compares favorably with the computed average of 31.3 per cent of seventeen other American centers. This also holds true for the recovery rates within the individual diagnostic groups.[14] The results of surgical intervention on only the orbital quadrants in these patients appear at least equal to the results obtained with transection of all four quadrants. The incidence of transitory postoperative urinary incontinence was found to be considerably lower (18 per cent) for the patients with the modified section of the orbital quadrants than for patients with section of all four quadrants (50 per cent).[10] In the postoperative course the dulling and slowing were less pronounced with the modified operation.

Freeman and Watts[10] (page 81) observed that placement of the cores in the lower part of the frontal lobes produced a higher incidence of good results than cores placed in the upper part of the frontal lobes. The significance of the orbital areas is apparent in the development of the surgical treatment of mental disorders. The various methods have progressed from the convexity of the prefrontal region to its subcortical strata, and finally to its orbital strata. The relation of emotional changes to lesions of the orbital area and the constancy of these lesions in 11 reported cases of changes in character, including the famous crowbar case of Harlow, were first pointed out by Welt[15] (1888). From a statistical study of 785 cases of cerebral tumors, Schuster[16] (1902) had the impression that involvement of the orbital lobes was to a higher degree responsible for the occurrence of emotional changes. The role of the orbital lobes in emotional changes becomes apparent from Berger's[17] work (1923). His material comprised chiefly bilateral prefrontal lesions (tumors, abscesses, injuries) within the brain substance or originating from the basal dura, such as tumors of the olfactory groove. He concluded that damage to the orbital lobes, especially to Brodmann's area 11, would without exception result in changes in personality.

From a study of vascular lesions of the brain, Alford[18] (1933) inferred that emotional disturbances were due to basal injuries. Kleist[19] (1937) attributed a central function in the emotional life to the orbital surface. Lemke[20] (1936) concurred in the opinion that changes in personality were particularly likely to appear in cases of tumor near the orbital surface. Grünthal[21] (1936) asserted that emotional disturbances and anomalies of behavior occur after trauma to the basal surfaces of the frontal lobes. In cases of Pick's disease he referred the initial lack of affective self control to damage to the orbital prefrontal area. Spatz[22] (1937) concluded that

TABLE 5.—*Status of Patients Following Bilateral Prefrontal Lobotomy (May 1942 to June 1944)*

	Subcortical Transection of Lower Quadrants					Subcortical Transection of Upper and Lower Quadrants					
Disease	No. of Patients	Patients Regularly Employed	Patients Partially Employed	Patients Able to Keep House	Patients Institutionalized	No. of Patients	Patients Regularly Employed	Patients Partially Employed	Patients Able to Keep House	Patients Institutionalized	Total No. of Patients
Affective reaction types	3	1	..	2	..	..	..	..	..	..	3
Obsessive tension states	1	..	..	1	..	..	..	..	..	..	1
Psychoneuroses	1	..	..	1	..	1	..	..	..	1	2
Epilepsy with psychosis	2	..	1	..	1	2	..	..	..	2	4
Schizophrenia	15	2	..	4	9	5	1	..	..	4	20
Total	22	3	1	8	10	8	1	..	..	7	30

14. Walker, A. E.: Psychosurgery: Collective Review, Internat. Abstr. Surg. **78**:1, 1944; in Surg., Gynec. & Obst., January 1944.

15. Welt, L.: Ueber Charakterveränderungen des Menschen infolge von Läsionen des Stirnhirns, Deutsches Arch. f. klin. Med. **42**:339, 1888.

16. Schuster, P.: Psychische Störungen bei Hirntumoren, Stuttgart, F. Enke, 1902.

17. Berger, H.: Klinische Beiträge zur Pathologie des Grosshirns: I. Herderkrankung der Präfrontalregion, Arch. f. Psychiat. **69**:1, 1923.

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20. Lemke, R.: Ueber doppelseitige Hirntumoren, Arch. f. Psychiat. **106**:54, 1936.

21. Grünthal, E.: Ueber die Erkennung der traumatischen Hirnverletzung, Berlin, S. Karger, 1936, p. 76; Ueber ein Brüderpaar mit Pickscher Erkrankung, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:350, 1930.

22. Spatz, H.: Ueber die Bedeutung der basalen Rinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **158**:208, 1937.

lesions of the "basal cortex," meningiomas, atrophy associated with Pick's disease, contusions and dementia paralytica lead to emotional changes and referred to the importance of the "basal cortex" for the functions of the "human psyche." In his recent detailed study on 32 cases of tumor, Rylander [23] (1939) obtained evidence that the basal parts of the frontal lobe play an important role in the emotional life, since 24 of his patients with parts of the orbital region removed showed emotional changes.

These results support the assumption that the basal parts of the frontal lobes are integrated in the emotional life. Further evidence for their role in the regulation of emotion comes from the experimental work on animals. Bilateral experimental lesions of the base of the brain (prechiasmal) in cats, according to Fulton and Ingraham [24] (1929), produced predominantly emotional disturbances. After prefrontal lobectomies, Walker [25] (1938) observed degeneration in the dorsal medial nucleus of the primate thalamus which he showed has not only connections with the hypothalamus but a projection system of fibers to the orbital surface of the frontal lobes (areas 9, 10 and 12).

All these observations point to a special significance of the basal part of the frontal lobes for the regulation of emotion (Goldstein [26]). The effect of section of the orbital part of the prefrontal lobes on the emotional life of patients with mental disease appears to confirm the assumption of an important role of the basal part of the prefrontal lobes in the emotional mechanism (Lashley [27]) of emotion.

23. Rylander, G.: Personality Changes After Operations on the Frontal Lobes, London, Oxford University Press, 1939, p. 296.

24. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesion of the Base of the Brain (Pre-Chiasmal), J. Physiol. **67**:27, 1929.

25. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938.

SUMMARY

In a series of 22 patients with mental disorders, chiefly paranoid schizophrenia, a satisfactory therapeutic result was obtained with a modified technic of prefrontal lobotomy, in which only the orbital areas were sectioned.

The orbital areas of the frontal lobes seem to have a role in regulation of the emotions.

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27. Lashley, K. S.: Functional Determinants of Cerebral Localization, Arch. Neurol. & Psychiat. **38**: 371 (Aug.) 1937.

MENINGIOMA OBSTRUCTING THE FORAMEN MAGNUM

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Meningeal tumor obstructing the foramen magnum is relatively rare and until recently has seldom been diagnosed ante mortem. A survey of the literature up to 1937 reveals only 14 cases with adequate clinical records, in all of which the diagnosis was made at necropsy. In 1938 Cushing and Eisenhardt,[1] in their monograph, stated:

> Whether a meningioma arising from the basilar groove which must be overlain and concealed by a posteriorly dislodged medulla and its emerging nerves could be safely exposed and surgically enucleated must be left for further experience to determine.

They recorded 4 cases in which surgical treatment was attempted, in all of which the termination was fatal.

Since 1937 about 35 cases have been reported in which various kinds of tumors obstructing the foramen magnum were successfully removed. In at least two thirds of these cases the tumor was an upper cervical meningioma projecting into the foramen magnum or a supraforaminal tumor extending into the cervical space. The following authors made reports: Voss,[2] 4 cases; Gardner, Karnosh and McNerney,[3] 1 case; Fay,[4] 1 case; Lereboullet and Puech,[5] 2 cases; Ecker,[6] 1 case; Love and Adson,[7] 23 cases (all types of tumors); Friedman,[8] 2 cases; List,[9] 1 case (multiple meningioma).

In order to obtain unpublished cases of recovery, we questioned a number of neurosurgical clinics. Because of wartime difficulties many clinics were unable to review their records; the few responses showed a surprising number of cases of tumor involving the foramen magnum, as follows: the Lahey Clinic, 6 cases; the University of Michigan, 4 cases; the Jewish Hospital of Brooklyn, 7 cases; the Cleveland Clinic, 3 cases; the University of California, 2 cases, and the Temple University Clinic, 2 cases—a total of 24 cases with recovery. In addition, a number of fatal cases were reported. These figures show that tumor involving the region described is not so rare as a review of the literature indicates and that since Cushing's pessimistic observation in 1938 neurosurgical technic has been greatly improved.

Our study was prompted by a recent unusual case of meningioma of the basilar groove occurring in a critically ill patient who for several months presented serious problems of clinical management. Difficulties in the diagnosis of this syndrome involve the differentiation of a large number of conditions, such as amyotrophic lateral sclerosis, syringomyelia, combined sclerosis (dorsolateral spinal degeneration), neuronitis, bony deformities of the foramen magnum, atlas and axis (platybasia) and congenital myelodysplasia.

REFORT OF A CASE

History.—C. H., a flying instructor in the Army aged 23, had a past history of no importance except for an attack of "flu" a year before, when he was at a camp in Texas. He was treated with sulfonamide compounds, was in bed a week, and lost 10 pounds (4.5 Kg.) in weight. He had severe occipital headaches but no pain

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4. Fay, T.: Localization and Treatment of Lesions of the Spinal Cord, S. Clin. North America **18**:1577-1597, 1938.

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in the head or neck thereafter. He was still weak on return to work.

Six months later, in October 1942, he again lost appetite and weight, but thought that he was neurotic because of emotional strain and worry over several accidents among cadet students. He noted a tight, bandlike sensation about the abdomen and difficulty at times in starting urination.

In February 1943 he noticed progressive numbness and weakness of the left hand, felt too weak to ride his bicycle to work and had increasing difficulty in getting in and out of the airplane. His fingers became so numb that he could not button his clothes. The last day he flew (two weeks before our examination) he got out of the plane only after a great struggle, wheeled his bicycle home and collapsed on the lawn, the bicycle falling on top of him.

He was sent by plane from Texas to his home in Omaha on two weeks' leave. Tremor of the right hand then developed, with inability to write or feed himself; weakness of the legs and spasmodic involuntary jerking movements occurred, and breathing became very difficult.

Neurologic Examination.—There were paralysis of the left side of the tongue, with atrophy and fibrillations, and notable paresis of the neck muscles and the intercostal and diaphragmatic muscles. The patient was extremely dyspneic, using the accessory muscles of respiration. Examination showed spastic flexor paralysis with atrophy of both arms, which was most conspicuous in the muscles of the hand; fibrillation of the muscles of the shoulders; exaggerated tendon reflexes, and a Hoffmann reflex bilaterally. The abdominal and cremasteric reflexes were absent. The legs showed almost complete spastic paralysis, with exaggerated tendon reflexes, clonus and all the reflexes indicative of involvement of the pyramidal tract. The slightest stimulation produced extreme massive involuntary spasm. The results of sensory examination were hard to evaluate because of the patient's difficulty in breathing and talking. Hypalgesia of the left arm and the left side of the trunk was patchy and questionable. There was no spontaneous pain and no involvement of proprioceptive function.

Course of Illness and Further Studies.—The patient was immediately hospitalized, on April 5, 1943, with a working diagnosis of acute amyotropic lateral sclerosis, which was later ruled out by the results of the first examination of the spinal fluid, with its total protein content of 500 mg. per hundred cubic centimeters. Because of impending complete respiratory paralysis, the patient was placed in a respirator, where he remained almost continuously for three months.

For about sixty days further neurologic examination was difficult, since the patient could remain out of the respirator only a few minutes at a time. During April 1943 the motor paralysis remained about the same—spastic quadriplegia with little voluntary movement, chiefly a slight movement of the fingers and toes; conspicuous fibrillations, which were readily seen, and severe emaciation, the weight being probably about 110 pounds (49.9 Kg.). Definite sensory changes had appeared in the form of bilateral loss of pain sensation throughout the lower cervical and all the dorsal and lumbar segments. The sacral segments were not involved; touch sensation was well preserved. The patient overreacted to painful stimuli, describing them as a burning sensation (similar to the thalamic reaction).

In May weakness of the sternocleidomastoid and trapezius muscles with atrophy was noted on the left side. Severe spasmodic involuntary jerking movements of the lower extremities occurred frequently; but the intercostal muscles seemed to regain power, and the patient could remain out of the respirator for longer periods.

Routine examination of the blood and urine revealed nothing abnormal. Roentgenograms of the skull and the cervical portion of the spine showed normal structures. In addition to the sensory paralysis earlier described, the cervical segments as high as the second became affected. Vibration sensibility, position sense and astereognosis were impaired in the upper extremities. As noted, first examination of the spinal fluid showed a total protein content of 500 mg. per hundred cubic centimeters. A second examination, in May, revealed a pressure of 150 mm. of water, normal hydrodynamics and a total protein content of 250 mg. per hundred cubic centimeters. Cisternal puncture, twice attempted, yielded no fluid, and the unnatural resistance encountered suggested obstruction at the foramen magnum. A third spinal puncture, on June 10, revealed 170 mm. of water. On careful jugular compression, the pressure rose to 230 mm. and did not fall back to the initial reading; the fluid was slightly xanthochromic.

The impression at this time was that of a lesion involving the left side of the medulla, localized by the eleventh and twelfth cranial nerves and causing obstruction of the foramen magnum—either a tumor associated with syringomelia or an extramedullary growth. After neurosurgical consultation it was decided to defer operation because of respiratory embarrassment, but a course of high voltage roentgen ray treatments was begun. Slow improvement in respiratory function followed, and gradually the patient was able to get along without the respirator.

The patient was then sent home for thirty days, and forced nutritional measures were continued. Neurologic examinations revealed the same spastic quadriplegia, with atrophy and fibrillations. At times spasmodic movements of the neck occurred. A fourth examination of the spinal fluid showed evidence of complete spinal block.

Surgical Procedures.—The patient was returned to the hospital on Sept. 4, 1943, for a two stage operation. In the first operation, on September 6, Dr. J. Jay Keegan performed a suboccipital decompression with local anesthesia. The medulla was observed to be elevated, flattened and displaced to the right by a firm extramedullary tumor, presenting in the left side of the foramen magnum. A small piece removed for biopsy showed a typical meningioma (figure). Because of respiratory embarrassment removal was not attempted.

For a few days there were symptoms of meningeal irritation from blood in the spinal fluid, but the patient showed rapid improvement, especially in respiration. Motor and sensory paralysis improved within one month, so much that the patient could walk unassisted. By November functional recovery was almost complete; only the motor paralysis of the left eleventh and twelfth cranial nerves remained.

On November 15, at a second operation, a firm, nodular tumor was exposed in the foramen magnum, the main portion lying above the basilar groove, beneath the medulla, and a smaller portion projecting through the foramen magnum about 1 cm. into the spinal canal. Careful dissection completely freed the lower portion, but removal necessitated the sacrifice of some of the roots of the eleventh cranial nerve. Dissection was then extended around the upper, and larger, portion of the tumor, which was separated with

difficulty from the cerebellum and the basilar groove, to which it was firmly adherent and where it apparently had its origin. The firm, fibrous tumor was removed piecemeal, the total weight being 8 Gm. When dissection was completed, the flattened medulla and the left eleventh cranial nerve were quite free. The twelfth cranial nerve was not seen, and it was thought that it had been sacrificed during removal of the portion near the condyloid foramen.

parently, neither the eleventh nor the twelfth nerve was completely sacrificed at operation. The patient returned to full duty as an air pilot instructor in May 1944.

COMMENT

A review of symptoms and signs reported by the various authors shows no clearcut clinical

The tumor is composed of spindle-shaped cells, showing a conspicuous tendency to formation of whorls. Some areas were fibrotic, and psammoma bodies were present.

A diagnosis of meningioma of the left condyloid foramen compressing the medulla at the foramen magnum was thus established.

The patient recovered uneventfully and left the hospital in two weeks. He then went to Florida for the winter, rapidly gained weight up to 150 pounds (68 Kg.) and through swimming exercise became very muscular. Neurologic examination six months after removal of the tumor showed no abnormal signs except for slight atrophy of the posterior left half of the tongue and slight weakness of the left trapezius muscle. Apsyndrome for tumors in this location. Many patients, like ours, had no pain; quadriplegia, with both motor and sensory disturbance, was consistently present. Because of the rather large space of the cisterna magna the tumor may grow to considerable size before signs of block appear. Roentgenographic evidence is usually negative for tumor in this region but does exclude platybasia: intraspinal myelographic study may be

necessary. There is little consistency in the neurologic signs. Although in all cases spastic signs were present bilaterally, sensory signs were seldom, if ever, present, the condition thus simulating amyotrophic lateral sclerosis. In other cases conspicuous signs referable to the posterior columns pointed to combined system disease; in still other cases sensory dissociation of syringomyelic type was present. Astereognosis and cerebellar signs were likewise reported.

The most consistent symptoms and signs are attacks of suboccipital pain, followed by bilateral spastic paralysis and some form of sensory paralysis, with unilateral palsies of the lower cranial nerves and an increased protein content of the spinal fluid. If signs of block are present, the diagnosis is certain. In a few instances evidence of increased intracranial pressure was also noted.

Since studies of the spinal fluid are absolutely necessary for correct diagnosis, it is important to note that in many fatal cases reported the patient died within a few hours after spinal puncture. One of us (A. E. B.)[10] has described elsewhere the problem of cerebellar herniation and the hazards of lumbar puncture in cases in which diagnostic signs of obstruction of the foramen magnum appear. The danger of sudden respiratory paralysis from tumor in this region is ever present, and the difficulties in managing this complication are well illustrated by our case. This danger forced us to use a respirator for several months, a life-saving procedure in our opinion.

10. Bennett, A. E.: Cerebellar Herniation into Foramen Magnum, J. A. M. A. **100**:1922-1925 (June 17) 1933.

CONCLUSIONS

Up to 1937 no case of operative recovery from meningioma obstructing the foramen magnum had been reported. Our compilation of about 60 reported and unreported cases of recovery since that time shows that this tumor is not infrequent and that notable advance in neurosurgical management has occurred.

In a case of meningioma of the condyloid foramen reported here respiratory paralysis required management in a respirator for three months. Complete recovery followed a two stage operation.

The diagnosis of neoplastic lesions in this location is particularly difficult because the symptoms resemble those of many other disorders and there is no clearcut clinical syndrome. Study of the spinal fluid is a necessary part of the diagnosis, but spinal puncture is extremely dangerous.

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DIVERGENCE PARALYSIS AND HEAD TRAUMA

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We have been able to find the report of only 5 cases of divergence paralysis as a complication of head injury. Bielschowsky [1] recorded the case of a youth aged 17 who sustained a cerebral concussion six weeks before ophthalmologic examination. He began to see double at a distance a few days after the accident. Four weeks after he was first seen there was no alteration in his condition. Weed [1b] reported 4 cases, in 1 of which the paralysis persisted three years. In a series of 1,550 cases of head injury encountered in private practice, we found 6 cases of divergence paralysis. In view of the paucity of such reports, a brief summary of these cases may be of clinical value.

REPORT OF CASES

CASE 1.—A girl aged 11 years complained of headache, double vision and difficulty in reading which had followed an accident two years before. She had fallen when pushed, striking the back of her head. She was not unconscious at that time but spoke irrationally for a short period. She vomited after the accident, was confused and showed mental changes for several hours. She had frontal headaches, which became intensified with ocular and physical effort, was nervous and found it difficult to read because of ready ocular fatigue. Glasses did not improve her vision. Examination revealed divergence paresis; the ankle jerks could not be elicited even with reenforcement; the left knee jerk was more active than the right, and the abdominal reflexes were all readily exhaustible.

CASE 2.—A white woman aged 28 struck the back of her head on falling when a table slipped. She was unconscious for a short, but undetermined, period, vomited and began to see double soon after the accident. The double vision persisted up to the time of examination, eight days later. There was occasional convergence of the eyeballs. She also complained of paroxysmal pains in the back of the head and dizziness on attempting to sit up. Five days later she had a convulsive seizure. There were involuntary movements of the head from side to side, repeated chewing movements and occasional incoherent spontaneous utterances. No convulsive movements were reported. She recalled nothing after the spell cleared.

Her previous history included poliomyelitis at the age of 2 years, followed by paralysis from the waist down. She was still disabled but walked with the aid of crutches. There was no history of double vision prior to the accident.

Examination showed occasional spasms of convergence. Between such spasms the red glass test revealed a divergence defect in the nature of homonymous diplopia in the central field; the distance between the images became greater as the source of light was moved away from the eyes. There was no evidence of palsy of the abducens nerve. Residual signs of old poliomyelitis were prominent, with atrophy and severe impairment of movement in the lower limbs and absence of reflexes. The patient complained of dizziness with passive movements of the head.

CASE 3.—A man aged 45 complained of having had headaches, dizziness, nervousness and double vision since an accident two years before, in which he was hit on the head by a steel hoisting cable and was thrown to the ground, striking his head. There was bleeding from the scalp and face. He was unconscious for fifteen minutes and vomited. He was hospitalized for three weeks. After leaving the hospital, he complained of recurring sharp pain in the back of the head every few hours, especially with bending and on attempting to read. The dizziness improved somewhat shortly after the accident. He had had ringing in both ears on and off since the injury. Double vision was noted immediately after the accident, especially on his looking at distant objects. He was irritable, with pronounced intolerance to noise. He became nauseated occasionally on bending. A month after he left the hospital, while sitting, he suddenly lost consciousness. Clonic movements were noted in the left upper extremity. He vomited after this seizure.

Examination showed that the blood pressure was 140 systolic and 74 diastolic and the pulse rate 72. There was a 3/8 inch (0.9 cm.) scar in the right parietal region and another scar, measuring 3/4 inch (1.9 cm.), below it. Auditory acuity was diminished on the left, with lateralization of the Weber sign to the left. The right pupil was slightly irregular and larger than the left; both reacted sluggishly to light and somewhat better in accommodation. The left palpebral fissure was the narrower. There was definite evidence of divergence paralysis. Studies showed concentric contraction of both fields. There was generalized hyperreflexia. The patient had amnesia for the accident and for a short period afterward. He was impatient and irritable.

CASE 4.—A man aged 41 six years previously was hit on the right ear while driving and was thrown out of the car. He was unconscious for an hour. A vertical linear fracture in the postparietal region just above the left mastoid was demonstrated roentgenographically. The patient complained of headaches, spells of dizziness and double vision, all dating from the accident.

Examination revealed divergence paralysis.

CASE 5.—A man aged 47 was driving a car when it collided with another. He was unconscious for ten minutes and remained in bed for six weeks. He complained of dizziness on bending his head. Double vision for distance had been present since the accident.

Examination three years after the trauma disclosed nerve deafness on the right side. A divergence defect was demonstrated with the red glass test.

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CASE 6.—A white woman aged 42 was struck on the head by a heavy valise which fell from a rack. She was unconscious for a short, but undetermined, period. There was bleeding from the nose; her face and right eyelid were swollen, and she vomited. She saw double for three weeks after the accident and still had diplopia occasionally.

The red glass test made fifteen months after the trauma disclosed homonymous diplopia in the central field; a hemisensory functional syndrome was also present on the right.

COMMENT

A review of 17,783 cases of acute and chronic head injuries reported in the literature from 1906 to 1943 [2] revealed no instances of divergence paralysis with the exception of the cases of Bielschowsky and Weed. Somberg [3] stated that no cases of divergence paralysis had been seen after head injury. Several authors indicated that diplopia was present but gave no explanation for it (Wortis and Kennedy [2r]). The absence of reports of divergence paralysis as a complication of head injury is possibly due to the fact that the patient is often too ill, especially in the acute stage, to be tested and, also, to the failure of the physician to make careful examinations to determine its presence. Aubineau [2a'] referred to 2 cases of disorders of associated movements of the eyes following head trauma but gave no details.

The question of the probable functional or hysterical nature of divergence paralysis has been discussed by von Hippel [2o'] and Clarke.[4] In our opinion, there is insufficient proof that this condition can occur on a hysterical basis. The appearance of divergence palsy after a psychic trau-

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ma does not prove its functional nature. Among over 2,000 cases of psychoneuroses observed in private practice, no case of divergence paralysis was encountered which could be considered entirely functional. In this material were represented many other functional ocular disturbances, such as amaurosis, tubular fields, ptosis, blepharospasm, monocular diplopia and convergence and accommodation spasm. There is no evidence that divergence palsy responds to forceful suggestive therapy or hypnosis. The association of functional sensory changes and other conversion phenomena does not prove the hysterical nature of the paralysis.

The presence of convergence spasm in case 2 raises the question whether divergence paralysis is really due to convergence spasm. The persistence of the homonymous diplopia for years, as in case 3, is somewhat against the theory of the existence of spasm. It is reasonable, also, to expect an insufficiency of convergence if spasm of this type is present. There was no evidence of such a defect of convergence in any of the patients examined.

We are of the opinion that in such cases the head trauma causes injury to the hypothetic center for divergence in the midbrain (Bender and Savitsky [2b']). In view of the persistence of the complaint in some of our cases (as long as five years after the injury), the lesion is occasionally irreversible, perhaps a laceration.

SUMMARY AND CONCLUSIONS

Six cases of divergence paralysis as a complication of head injury were encountered in a series of 1,550 personally observed cases of head trauma.

Only 5 similar cases were found among 17,783 cases of head injury reviewed in the literature.

We believe this syndrome is more common than has heretofore been indicated.

1882 Grand Concourse.

ELECTROENCEPHALOGRAPHIC EVALUATION OF PRIMARY BEHAVIOR DISORDERS IN CHILDREN

CORRELATIONS WITH AGE, SEX, FAMILY HISTORY AND ANTECEDENT ILLNESS OR INJURY

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In a number of reports it has been shown that there is a significant preponderance of the "too slow" type of electroencephalogram for children with disturbances diagnosed as primary behavior disorders. Jasper, Solomon and Bradley,[1] the first to report this observation, discovered that of a sample of 71 children, 73 per cent showed slow abnormalities. The finding has been repeatedly confirmed by a large number of investigators.[2] From this observation it appears that when a relatively new yardstick, the electroencephalogram, is applied, two forms of the disturbance appear: primary behavior disorders associated with a normal electroencephalogram, and primary behavior disorders associated with an abnormal electroencephalogram, the number of children with the latter at least equaling, and probably exceeding, the number with the former.

Records which are of the "too slow" type are frequently associated with epilepsy and are broadly related to psychomotor seizures.[3] It can be argued that the so-called primary behavior disorders with an abnormal electroencephalogram are in reality a hitherto undetected form of behavior disorder associated with epilepsy, or perhaps a variant of psychomotor epilepsy. In addition, it has been discovered that there are strong hereditary characteristics in the electroencephalograms of epileptic persons, a great proportion of the seizure-free parents of epileptic children exhibiting abnormal waves and, conversely, the seizure-free children of epileptic parents showing a considerable amount of abnormal electrocortical activity.[4]

Furthermore, head injury is known to result in abnormality of the electroencephalogram, as are also anoxia, encephalitis and other conditions leading to known cortical involvement,[3] independent of epilepsy. Consequently, it can be argued that any of these conditions might be associated with primary behavior disorders with abnormal electroencephalograms.

Since it cannot be told from the electroencephalogram, except in a restricted number of cases, whether the abnormality has its origin in genetic factors or in traumatic or infectious

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From the Iowa State Psychopathic Hospital and the State University of Iowa College of Medicine.

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cerebral injury, recourse to the history of the patient and of the patient's relatives is required to evaluate the etiologic factors in the record.

The present study is an extension of the previously reported observations and implications.

METHOD

Of a group of children with psychiatric disorders from whom electroencephalograms had been obtained, the conditions of 67 were diagnosed as primary behavior disorders. A definition of primary behavior disorders in children has never been adequately formulated. Kanner[5] pointed this out in his discussion of the problem of nosology for children when he stated:

"The manifoldness and complexity of behavior disorders have made systematic grouping extremely difficult. . . . This is especially true of children because personality is still in *statu nascendi* and any cataloging, therefore, can at best be anticipatory rather than conclusive." Yet of the all-inclusive group of behavior disorders in children, certain categories can be delimited in descriptive or etiologic terms, implying thereby laws which allow prediction. Among various outlines for the psychiatric classification of problem children is that of Brown, Pollock, Potter and Cohen,[6] which incorporates a combination of etiologic and descriptive nosology. Their principal groups are (1) mental deficiencies; (2) psychoses; (3) psychoneuroses and neuroses; (4) convulsive disorders, including epilepsy; (5) behavior disorders with somatic disease or defect; (6) psychopathic personalities; (7) educational disabilities; (8) primary behavior disorders; (9) social problems, and (10) other problems. We follow their nosology, so that our definition of primary behavior disorders coincides with theirs except that we incorporate their group of psychopathic personalities in our definition. This occurs because we are unable to differentiate these two groups on either a descriptive or an etiologic basis. Primary behavior disorders cannot be thought of as constituting a specific entity but are to be regarded as a heterogeneous collection of disorders formed as a result of the exclusion of other, better described, groups.

Criteria for inclusion of cases in the present study were a composite record of the psychiatric, physical, neurologic, laboratory and psychometric examinations and a detailed social history. The social histories were comprehensive and were obtained primarily from one or both parents; in a few cases they were obtained from a person, other than the parents, who accompanied the child to the clinic. In most instances this material was supplemented or corroborated by social agencies, physicians, teachers, friends or other nonfamily members. No case was included in which the symptoms were suspected of being sequelae of a physical illness or injury.

From these collected data it was then possible to investigate the relation of the electroencephalogram to factors of age, sex, family history and antecedent injury or severe illness.

The group included children of both sexes and ranged in age from 6 through 15 years. All the children had intelligence quotients above 80 on the revised form of the Stanford-Binet intelligence test. Physical examination of these 67 children at the time they were studied indicated no recognized relation to the behavioral problems presented. The most common and frequent findings were carious teeth, malnutrition, underdevelopment, enlarged tonsils, acne, visual refractive errors and obesity. One child had chronic bronchitis. In another youngster rheumatic fever with cardiac involvement developed while he was being treated in the hospital (but after our examinations), and he was transferred to the pediatric ward. Another child had bilateral deafness.

From the detailed history obtained for each child certain data were selected and used as criteria for the designation of the family history as positive or negative. Preliminary examination of the histories revealed four ancestral types which could be clearly defined and labeled as positive, on the basis of the presence of one of the following disorders: (1) psychosis, (2) maladjusted personality (this was sometimes difficult to determine, but a positive decision was made if the person involved had reputedly never been able to make an adjustment because of inability to control his emotional responses, and hence was in repeated difficulties), (3) chronic alcoholism (this was selected because of the relative rarity of this condition in this section of the country [Iowa], and its almost constant association with severe personality maladjustment) and (4) epilepsy. In most instances a positive history included the occurrence of the condition in a parent or grandparent, the history only rarely being called positive on the basis of the involvement of a collateral line.

The antecedent illnesses and injuries which were selected for consideration were (1) prematurity, (2) birth injury or questionable birth injury, (3) head injury complicated by unconsciousness, (4) severe illness complicated by delirium, (5) convulsions in infancy (a single, isolated convulsion not believed to be of epileptic origin) and (6) a period of anoxemia, either at birth or later in life.

Six lead electroencephalograms were made for virtually all subjects (in rare cases three lead records were obtained), monopolar recordings being made from the left and right occipital, motor and frontal regions of the skull. Records were made with the subject relaxed and the eyes closed. Small lead pellets, secured to the end of a fine enamel-insulated wire, were cemented to the scalp with collodion, an electrode jelly of the electrocardiograph type being used to enhance conductivity. A three channel, ink-writing oscillograph recorded the electroencephalogram. All recordings were at least eighteen minutes in length.

In analysis of the electroencephalographic records a subjective classification was employed, since no absolutely quantitative norms are as yet available for children. A preliminary inspection of all of the records indicated that it would be possible to place each record into one of a series of categories. The entire series of records was then reviewed and assigned, on the basis of experience in obtaining records from 270 unscreened normal children (by one of us, J. R. K.), to its appropriate class. The most thorough quantitative data on what constitutes the normal electroencephalogram in children have been published by Lindsley,[7]

5. Kanner, L.: Behavior Disorders in Childhood, in Hunt, J. M.: Personality and the Behavior Disorders, New York, The Ronald Press Co., 1944.

6. Brown, S.; Pollock, H. M.; Potter, H. W., and Cohen, D. W.: Outline for the Psychiatric Classification of Problem Children, Utica, N. Y., State Hospital Press, 1937.

7. Lindsley, D. B.: A Longitudinal Study of the Occipital Alpha Rhythm in Normal Children: Frequency and Amplitude Standards, J. Genet. Psychol. **55**:197-213, 1939.

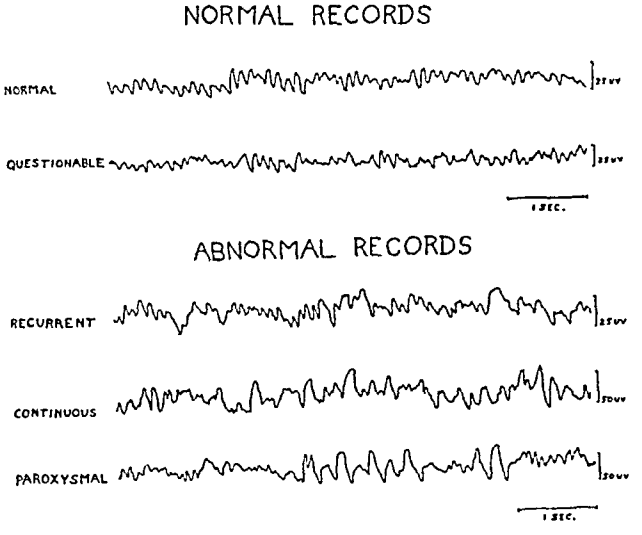
who determined the variation of frequency limits with age. These limits were used to define an electroencephalogram as "normal." Gibbs and Gibbs[3] published an essentially qualitative chart of the relative incidences of slower than dominant frequencies in the electroencephalogram at various ages. This chart and the experience of one of us (J. R. K.) were used to classify a record as other than normal.

The exact classification is, of course, essentially subjective. Definitions of the categories follow.

1. Normal: Records within the normal frequency limits derived from Lindsley's age frequency table.

2. Questionably normal: Records presenting not only the dominant frequency for the age expected, but either too slow or too fast frequencies nondominant, but present to a sufficient extent to make difficult the qualitative estimate of a normal record. (Such records are not included in the final statistical treatment of these data because of their uncertain allocation; clinically we consider these electroencephalograms "normal" in order to be conservative.)

3. Abnormal: Records presenting dominant frequencies above or below the age norm. These frequencies



Sample strips of electroencephalograms, illustrating the characteristic features of the record in each electroencephalographic category. At the left of each strip is the name of the category as defined in the text. At the right is the calibration for microvolts and for one second.

These sample strips were all obtained from patients 8 years of age. For different ages the normal frequencies vary, being slower for the younger and faster for the older children, but the relative differences among the categories remain the same.

may appear (*a*) recurrently, in long bursts of several seconds; (*b*) continuously, with no normal frequencies present, or (*c*) paroxysmally, as a sudden change to a seizure-like pattern, but usually occurring against a dominant background of normal activity; it could, and sometimes did, occur against a continuously too slow background, when the record was classified as "paroxysmally abnormal."

The figure presents samples of records illustrating each category. This classification was applied only to the "resting" record. No record obtained during or after hyperventilation was used in this study.

DATA

The electroencephalograms for the 67 patients were classified as follows:

Normal	27	(40 per cent)
Questionably normal	7	(10 per cent)
Recurrently abnormal	18	(27 per cent)
Continuously abnormal	8	(12 per cent)
Paroxysmally abnormal	7	(10 per cent)

If the last three categories are combined, 33 patients (49 per cent of the series) had abnormal records. Hereafter this combined group will be considered as a unit. This percentage is slightly lower than, but consistent with, the percentage reported by other investigators[8] for children with primary behavior disorders and is considered higher than the percentage to be expected from a group of unscreened but presumably normal children.[9] The fact that our percentage of abnormal records for the entire series is lower than that reported by other authors may be attributed to our attempt to exclude all known or probable conditions of organic origin at the outset.

TABLE 1.—*Analysis of the Electroencephalogram in Relation to Age and Sex*

	Encephalograms						
	Males			Females			
Age	Abnormal	Questionably Normal	Normal	Abnormal	Questionably Normal	Normal	Totals
6	1	..	1	..	..	..	2
7	..	..	1	..	..	1	2
8	3	2	3	1	..	..	9
9	..	1	1	..	..	1	3
10	..	..	3	1	..	..	4
11	1	..	1	2	..	..	4
12	3	1	2	1	..	..	7
13	8	1	..	..	..	..	9
14	4	..	5	1	1	3	14
15	4	1	5	3	..	..	13
Totals	24 (46%)	6 (12%)	22 (42%)	9 (60%)	1 (7%)	5 (33%)	67

Table 1 presents an analysis of the electroencephalograms in relation to age and sex. The distribution for age shows a greater percentage in the upper levels, for 36 (54 per cent) of the patients were in the age groups of 13, 14 and 15 years. There is an apparent difference in the percentage of abnormal electroencephalograms

8. Jasper, Solomon and Bradley.[1] Lindsley and others.[2]

9. In a personal communication Mr. C. E. Henry, who has over 2,000 electroencephalographic records on an unscreened group of children, stated that the percentage of abnormal records, with essentially the same classification, was approximately one-half ours. For a group of 270 unscreened children, records on whom were made by one of us (J. R. K.), this percentage was approximately one-quarter the value for the group considered in the present report.

between the younger and the older age groups. Statistically, however, the difference in the distribution of the types of electroencephalograms of patients younger and of patients older than 12 years of age is not significant at the 5 per cent level, and one need not reject the hypothesis that the two distributions are the same. Other investigators [2] have reported that there is a greater incidence of abnormalities in younger than in older patients. This is at variance with the tendencies of our data, even though these tendencies are themselves insignificant. Perhaps the explanation lies in the judgments of normality employed in the various investigations, for at earlier ages there is normally frequent slow activity.

Fifty-two (77 per cent) of the patients were males, a ratio of 3:1. There were no statistically significant differences in regard to the distribution of abnormal or normal electroencephalograms for the two sexes. Thus, the data

TABLE 2.—*Analysis of the Electroencephalogram in Relation to Family History and Antecedent Severe Illness or Head Injury*

	Electroencephalograms		
		Questionably	
	Abnormal	Normal	Normal
Family history only	9 (48%)	5 (26%)	5 (26%)
Illness or injury only	7 (54%)	.....	6 (46%)
Family history and illness or injury	13 (65%)	1 (5%)	6 (30%)
No positive family history or previous illness or injury	4 (27%)	1 (6%)	10 (67%)
Totals	33 (49%)	7 (11%)	27 (40%)

in this table indicate that age and sex are not significant factors in relation to the electroencephalographic characteristics observed.

Table 2 presents an analyses of the electroencephalograms in relation to antecedent illness, injury and/or family history. Thirty-nine patients (58 per cent) had a positive family history, and 33 (49 per cent) had a positive history of illness or injury. The striking feature in this table is the difference between the patients who had neither a positive family history nor any significant antecedent illness or injury and the patients who had both a positive family history and a history of illness or injury. Of the former group, 4 patients (27 per cent) had abnormal electroencephalograms, in contrast to 13 patients (65 per cent) of the latter group. Although the absolute number of patients is small in each group, it was possible to subject the two distributions to a statistical treatment to discover whether they differed significantly. With the method of χ^2, a level of significance of 3 per cent was obtained. This means that the difference could be attributed to chance in only 3 out of 100 experiments and is thus statistically significant.

Further examination of this table indicates that 9 patients (48 per cent) had abnormal electroencephalograms in the group with a positive family history only and 7 (54 per cent) in the group with a history of antecedent illness or injury alone. When the distributions for the group with a positive family history and the group with neither a positive family history nor a history of illness or injury were compared by the χ^2 test, the difference was found to be significant between the 5 and 10 per cent levels of confidence. When the distributions for the group with antecedent illness or injury and the group with neither a positive family history nor antecedent illness or injury were compared, the level of significance as revealed by the χ^2 test fell between 5 and 2 per cent. The first comparison may be regarded statistically as strongly suggesting that the two distributions differ, while the second is acceptable as indicating that a true difference does exist.

TABLE 3.—*Analysis of the Electroencephalogram in Relation to Positive Family History*

	Electroencephalograms		
		Questionably	
Family History	Abnormal	Normal	Normal
Psychosis only	2	1	2
Psychosis and maladjusted personality	1	3	1
Psychosis and alcoholism	1	..	..
Psychosis and epilepsy	1	1	..
Totals	5	5	3
Maladjusted personality	9	1	3
Maladjusted personality and psychosis	1	3	1
Maladjusted personality and alcoholism	1	..	2
Maladjusted personality and epilepsy	1	..	..
Totals	12	4	6
Alcoholism	3	..	2
Alcoholism and psychosis	1	..	..
Alcoholism and maladjusted personality	1	..	2
Alcoholism and epilepsy	1	..	..
Totals	6	..	4
Epilepsy	2	..	1
Epilepsy and psychosis	1	1	..
Epilepsy and maladjusted personality	1	..	..
Epilepsy and alcoholism	1	..	..
Totals	5	1	1

Thus these data indicate that the abnormal electroencephalograms are related both to the selected factors in the family history and to illness or injury sustained early in life. When both factors are present, the level of significance is higher than when either factor operates alone.

The further problem then appears: Are certain of the selected criteria for a positive family

history, or for the personal history of illness or injury of the patient, closely related to electroencephalographic abnormality, and are certain others not? The data pertaining to this question are presented in tables 3 and 4. The number of cases is too small to allow the application of statistical technics; yet by inspection the data are of interest. Table 3 presents a summary of the electroencephalographic data in relation to the four selected categories of disorders in the family history: psychosis, maladjusted personality, chronic alcoholism and epilepsy. Two groups of patients, those in whose family history there was either epilepsy or maladjusted personality, stand out as having a relatively higher percentage of abnormal electroencephalograms than the other two groups.

TABLE 4.—*Analysis of the Electroencephalogram in Relation to Antecedent Illness or Head Injury*

Illness or Injury	Electroencephalograms: Abnormal	Questionably Normal	Normal
Prematurity and birth injury...	2	..	1
Prematurity and head injury...	1	..	..
Totals	3	..	1
Birth injury	1	..	1
Birth injury and prematurity...	2	..	1
Birth injury and severe illness...	1	..	2
Birth injury and convulsions....	..	..	2
Totals	4	..	6
Head injury	1	..	..
Head injury and prematurity...	1	..	..
Head injury and severe illness...	2	1	..
Head injury and convulsions....	1	..	..
Totals	5	1	..
Severe illness	8	..	6
Severe illness and birth injury...	1	..	2
Severe illness and head injury...	2	1	..
Severe illness and convulsions...	1	..	..
Totals	12	1	8
Convulsions	2	..	..
Convulsions and birth injury...	..	..	2
Convulsions and head injury....	1	..	..
Convulsions and severe illness...	1	..	..
Totals	4	..	2

Table 4 presents a summary of the electroencephalograms in relation to the five selected categories for illness and injury in the personal history: prematurity, birth injury, head injury, severe illness and convulsions. It is here seen that head injury is more closely associated with electroencephalographic abnormality than are the other factors. Whether these differences in tables 3 and 4 are due to chance or are true differences cannot be stated until further data are at hand, but the implications are worthy of investigation.

COMMENT

All the data which have been reported on the electroencephalographic abnormalities associated with primary behavior disorders in children suggest that that category may be subdivided into two types: primary behavior disorders with normal electroencephalograms and primary behavior disorders with abnormal electroencephalograms. The present data add another confirmatory link to a long chain of such evidence. In addition, they suggest the excellent probability that the second type can itself be further divided into two, or perhaps three, subtypes: one in which the abnormal electroencephalogram may be related to the family history, and thus by inference is probably hereditary; a second, related to illness or injury, sustained early in life (and of such a nature as to have been considered noncontributory to the behavioral disturbance), and a third, in which both factors may be believed to operate. Confirmation of the first of these proposed additional subtypes can be obtained directly, by investigations in which the electroencephalograms of both the parents and the progeny are recorded and are correlated with the family history. It is probable that some parents not considered to furnish "positive" evidence according to the evaluation of the social histories will show abnormalities in the brain potentials, the presence of which will extend the scope of the hereditary implications of the abnormal electroencephalogram. At present we are engaged in such an undertaking.

The implications of the abnormal record are clear, for one can only conclude that there is some pathophysiologic cortical process. The implications of the normal electroencephalogram are, in a sense, equally clear, that there is no pathophysiologic cortical process. It is of course necessary that these implications be considered in terms of the probability theory, for it is known that such a process may be dormant at the time of recording, and thus not be made apparent on the record. Furthermore, assumptions of the presence or absence of a pathophysiologic process can at present be referred only to the cortex. Subcortical processes may not be normal; yet the electroencephalogram may be repeatedly without discernible abnormal activity. (Deep lesions, for example, may be proved to be present and the electroencephalogram be normal.) Therefore one must consider the probability that an unknown number of patients present primary behavior disorders with normal electroencephalograms and still have pathologic neural function.[10]

10. These statements are not in exact accord with the recent experimental observations of Kennard (Effects on the Electroencephalogram of Chronic Lesions of Basal Ganglia, Thalamus, and Hypothalamus of Monkeys, J. Neurophysiol. **6**:405-415, 1943) on the mon-

(Footnote continued on next page)

Such a pathophysiologic process may be causally ascribed to several possible factors. Schreiber [11] presented evidence indicating that of 500 children showing neuropathologic changes, 70 per cent had had a period of prolonged apnea at birth. This clinical finding has been substantiated by direct experimental test, by Windle and Becker,[12] with the guinea pig as subject. Another factor has been indicated by Lurie and Levy,[13] who reported that the occurrence of pertussis before the age of 2 years is of importance in determination of subsequent patterns of behavior. Hence, perhaps more emphasis may be placed on factors of previously unsuspected or nonevaluated importance, particularly in cases in which the electroencephalogram does not meet standards of normality.

This approach appears definitely organic, but one can never successfully deny the tremendous importance of the social environment on the developing organism. However, unless the environment is limited and rigid, the individual organism has some freedom of selection from among the various social environments which present themselves to him. Out of this variety a child can choose that which meets his needs. Hence, a poor environment surrounding a given child may be the result of factors influencing his processes of selection (his own motivational processes, or needs). Furthermore, the child does make an impact on his social surroundings, and the impact involves energy on both sides of the equation: The environment acts back on the child according to the characteristics of the impact initiated by him. In turn, there is, then, further impact on the reacting environment, and a great spiral of activity takes place. Even if the initial impact is that of society on the child, the individual factors present within the child determine the consequent development of the spiral reacting processes.

The electroencephalographic data appear to indicate that there are discoverable and repeatedly verifiable organic processes in some of the heterogeneous group of disturbances diagnostically categorized as primary behavior disorders. If these organic processes are regarded as contributory to the disorder, such evidence affords considerable support to persons who subscribe to a view of constitutional determination of behavior patterns. However, the present data suggest that these constitutional variables be so defined as to include genogenic factors and characteristics acquired early in life, as a result of chemogenic or histogenic experiences which permanently alter the response tendencies of the organism. It has been proposed [14] that the pattern of the electroencephalogram is determined constitutionally, but it has been suggested [15] that such arguments should be limited to specific frequency bands of the electrocortical continuum which are known to be related to genogenic, histogenic and chemogenic factors. With such a restriction, it follows that abnormal (i. e., excessive slow or fast) activity may represent some aspect of the neural limits of the behavior of the organism, i. e., the variables limiting the range of the selection process and the variables determining the environmental tolerance levels.

We conclude from our data that these neural limits may be set by genetic and certain environmental factors and that the evaluation of a given patient depends entirely on the relative strength of the evidence in each of the possible contributory spheres: ancestral transmission, early physical trauma and social trauma.

CONCLUSIONS

1. As has frequently been shown, there is a high incidence of abnormality in the electroencephalograms of children with primary behavior disorders. In the present series of 67 children, none of whom presented signs of organic disease or in whose condition an organic etiologic factor was suspected, 49 per cent had electrical brain potentials which were clearly abnormal.

2. Age and sex were unrelated to electroencephalographic abnormality.

3. Significantly greater proportions of abnormal electroencephalograms were found when there was either a history of psychosis, maladjusted personality, chronic alcoholism or epilepsy in the family or a personal history of cerebral trauma or severe illness than when neither of these factors was present.

key, which indicate that induced cortical lesions may have no reflection in the electroencephalogram, while lesions in the thalamus and hypothalamus may indeed be reflected in the electrocortical records. There seems, therefore, to be disparity between clinical experience and experimental fact.

11. Schreiber, F.: Apnea of the Newborn and Associated Cerebral Injury, J. A. M. A. **111**:1263-1269 (Oct. 1) 1938.

12. Windle, W. F., and Becker, R. F.: Asphyxia Neonatorum: Experimental Study in the Guinea-Pig, Am. J. Obst. & Gynec. **45**:183-200, 1943.

13. Lurie, L. A., and Levy, S.: Personality Changes and Behavior Disorders of Children Following Pertussis, J. A. M. A. **120**:890-894 (Nov. 21) 1942.

14. Davis, H.: Some Aspects of the Electrical Activity of the Cerebral Cortex, in Cold Spring Harbor, Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, pp. 285-291.

15. Knott, J. R.: Electroencephalography and Physiological Psychology: Evaluation and Statement of Problem, Psychol. Bull. **38**:944-975, 1941.

SUBDURAL SUPPURATION ORIGINATING IN PURULENT LEPTOMENINGITIS

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In the course of routine autopsies we have observed occasional cases of subdural suppuration (figs. 1 and 2) which is apparently secondary to an underlying leptomeningitis. We wish to eliminate from this discussion all cases of subdural infection secondary to causes other than underlying disease of the leptomeninges. Specifically, we exclude subdural suppuration secondary to extension from diseased paranasal sinuses, mastoid air cells and the middle ear. Similarly, we exclude from consideration subdural infection arising from a penetrating cranial injury, infected subdural hematoma and osteomyelitis of the skull.

REVIEW OF LITERATURE

A diligent search of the literature failed to reveal any papers on this subject except for a single article by Bateman, in 1929.[1] In this report there is a passing reference to subdural suppuration secondary to involvement of the pacchionian granulations in cases of purulent leptomeningitis.

PRESENTATION OF CASES

In a series of 95 consecutive cases of leptomeningitis encountered in a total of 4,756 autopsies at the Queens General Hospital, only 2 with subdural involvement satisfied our previously stated criteria. Although apparently rare, subdural suppuration probably occurs much more frequently than our figures indicate. More careful gross and microscopic examination of the dura in all cases of leptomeningitis should bear out this assumption.

CASE 1.—A white man aged 61 was admitted to the hospital one month before his death with the complaint of weakness and eructation. The past history was noncontributory. The history of the present illness was unclear and largely irrelevant, as the patient had neither signs nor symptoms of meningitis at the time of admission. Recurrent attacks of painless jaundice had been present for six months. This was followed by the eventual development of the classic signs of neoplastic obstruction of the common bile duct.

Physical examination on admission revealed emaciation, cachexia and anemia, with a tender mass in the right upper part of the abdomen and a palpable liver.

The patient was awaiting operation when his temperature suddenly rose to 101 F. and then to 105 F. He complained only of headache, first mild and then severe. The following day he fell out of bed. When picked up, he seemed confused and disoriented. Examination showed no signs of injury, although he groaned when his head was moved. Ten hours later he passed into shock, and pulmonary edema developed, the patient dying almost immediately.

Fig. 1.—Subdural suppuration, gross appearance.

Necropsy failed to reveal any signs of cerebral trauma. The inner surface of the dura presented an adherent purulent membrane, measuring 10 by 6 by 0.2 cm., over the left parietal region. The subdural space contained a marked excess of cloudy fluid, from which a type VIII pneumococcus was recovered. There was a thick green subarachnoid exudate over the vertex and the cerebellum. The sphenoid sinuses and the middle ears were normal. The left ethmoid sinus contained a drop of cloudy fluid, from which Bacillus coli was cultured. Autopsy revealed that there was no connection between this infection and the subdural exudate.

From the Department of Pathology, Queens General Hospital,

1. Bateman, J. F.: Meningitis with Special Reference to the Role of the Pacchionian Bodies, Ohio State M. J. **25**:970-976, 1929.

The other autopsy observations were severe pancreatitis, with pronounced fibrosis and tendency to abscess formation, and a small carcinoma of the head of the pancreas, partially obstructing the common bile duct.

Microscopic examination confirmed the gross observation of subdural and leptomeningeal infection. The pacchionian granulations were intensely involved in the inflammatory process, with extension into the subdural space (fig. 3*A* and *B*).

CASE 2.—A white boy aged 3 years was admitted to the hospital seven weeks before his death. The history was noncontributory. The child was admitted moribund and with great respiratory difficulty. Only a hurried physical examination was possible. An emergency tracheotomy was performed. For several days after the operation he had a high temperature. The fever could not be adequately explained, as the only physical signs during this interval were those of a mild infection of the upper respiratory tract. There were no signs of otitis media. On the seventh day he had obvious meningitis. Haemophilus influenzae was grown from the purulent spinal fluid. For the next six weeks he showed evidence of chronic purulent meningitis, with no decided change in his condition. Culture of repeated specimens of the spinal fluid yielded the same organism. At the end of six weeks he became worse suddenly, passing into coma and showing rigidity of the extremities, especially on the left side. After this sudden change, the course was rapidly downhill, death occurring after seven weeks of illness.

Necropsy revealed a 2 cm. area of adhesions between the dura and the arachnoid over the right frontal region. Microscopic sections taken through this area showed a purulent exudate in both the subarachnoid and the subdural spaces. The arachnoid membrane was necrotic and partially destroyed. Diffuse purulent leptomeningitis with prominent hydrocephalus was also present. The middle ears and the sinuses were free of infection. Of particular interest was the necrotizing involvement of the bridging vessels, particularly the veins, which in some cases had allowed their infected contents to escape through their damaged walls (figs. 2 and 4).

In 3 other cases of our series we observed subdural purulent inflammation together with purulent leptomeningitis. A complicating factor in each of these cases was the presence of a coexistent infection of the middle ear or the paranasal sinuses. In each case we were able to culture a pneumococcus from both the subarachnoid and the subdural spaces, and significantly, we could culture only a streptococcus, a staphylococcus or Bacillus pyocyaneus from the middle ear or the sinuses. Therefore we are certain that these cases represent an extension of antecedent leptomeningitis into the subdural space. However, because of the complicating

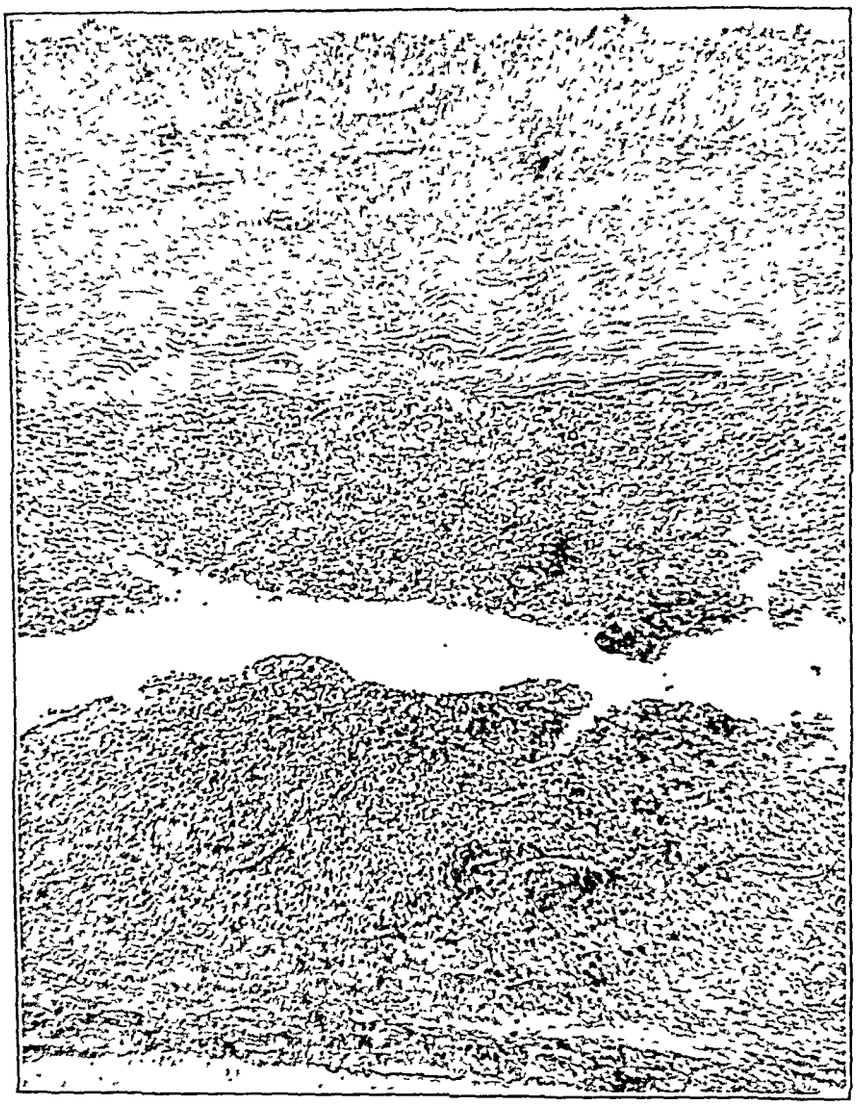

Fig. 2 (case 2).—Subdural empyema following necrosis of the arachnoid with extension into the subdural space; × 100.

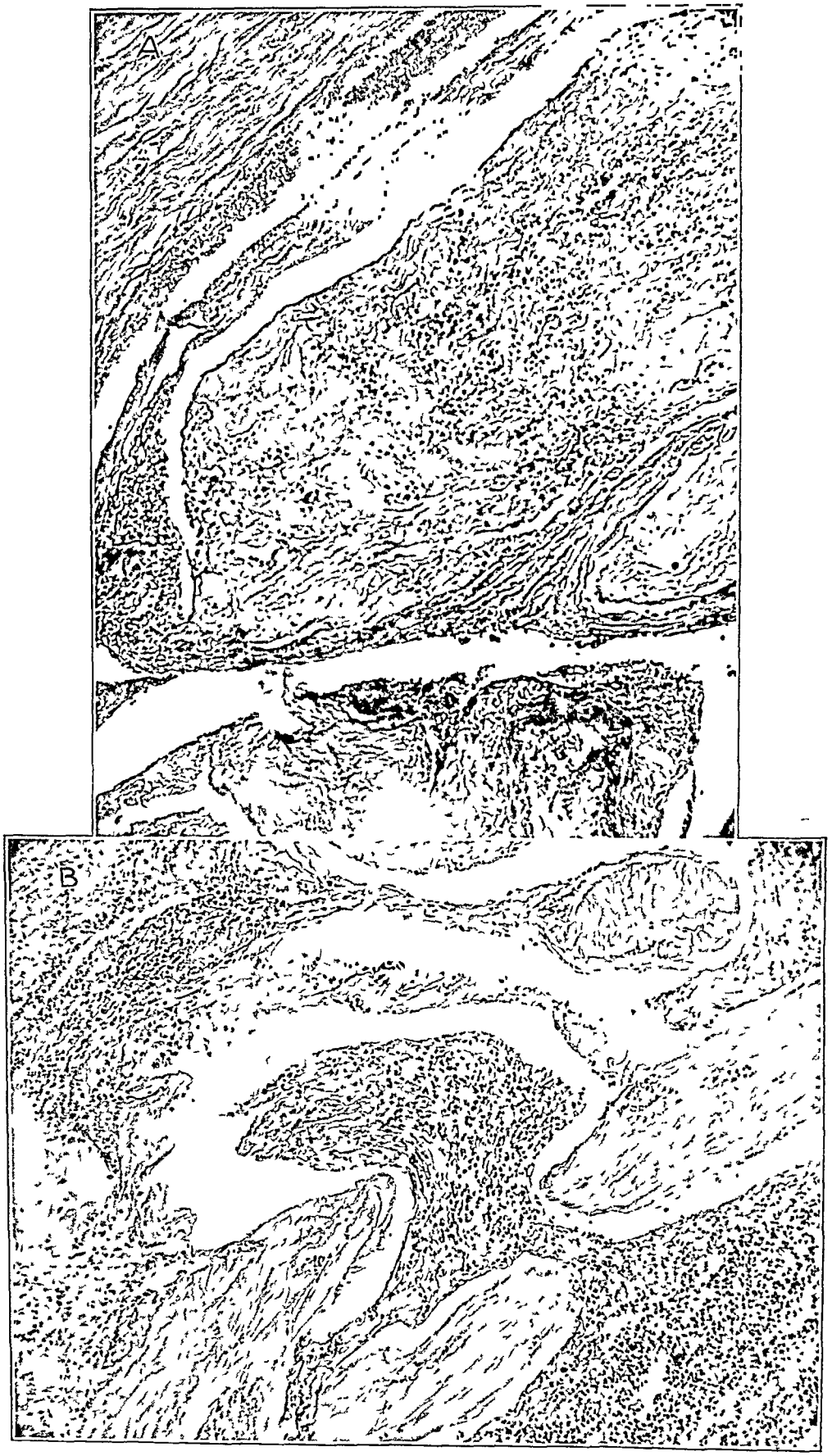

Fig. 3 (case 1) —*A*, massive involvement of the arachnoid villus, with beginning extension into the subdural space. *B*, massive involvement of the arachnoid villus, with beginning extension into the subdural space; × 100.

infection of the sinus or the middle ear, they fail to satisfy the introductory criteria for inclusion in our group of cases.

PERTINENT ANATOMIC RELATIONS AND MECHANISMS OF EXTENSION

The gross and microscopic anatomy of the meninges has been described by Weed [2] in some detail. However, a brief review of the pertinent histologic features, with especial reference to the mesothelial elements involved, will serve to clarify further discussion (fig. 5).

Fig. 4 (case 2).—Extensive phlebitis in a bridging vein; × 440.

The brain is covered by three membranes. The innermost layer, the vascular pia, is applied directly to the surface of the brain. The outer layer of the pia consists of a single, incomplete layer of mesothelial cells (*A*). The second membrane, the arachnoid, consists of connective tissue covered on the inner aspect by an incomplete layer of mesothelial cells (*B*). This mesothelium is continuous with similar mesothelium covering the trabeculae and blood vessels which traverse the subarachnoid space. The outer layer of the arachnoid, which is applied to the inner layer of the dura, consists of a complete mesothelial sheet (*C*). It is the subarachnoid space which contains the cerebrospinal fluid. The third membrane, or dura mater, consists of several layers of connective tissue with an innermost, complete mesothelial membrane (*D*). The outer surface of the dura is attached to the bones of the skull and is firmly adherent to the suture lines. The subdural space is therefore a potential space between two complete mesothelial membranes investing the outer aspect of the arachnoid and the inner surface of the dura (*E*).

The dural sinuses are venous channels lined by endothelium and formed by triangular separations of the layers of the dura. Along the dural sinuses, particularly the superior sagittal sinus, there are numerous outpouchings of arachnoid and mesothelium, known as arachnoidal villi (*F*). These villi project into the lumen of the sinuses and, in addition to their component

2. Weed, L. H.: An Anatomical Consideration of the Cerebrospinal Fluid, Anat. Rec. (supp.) **12**:461, 1917.

arachnoid connective tissue and mesothelium, are covered by layers of dural mesothelium and sinus endothelium. Consequently, the potential subdural space can be considered as continuous over the arachnoid villi and is separated from the interior of the villus by only two layers of mesothelium, one of which is incomplete.

The subarachnoid and subdural spaces are generally considered to have no points of communication. However, the arachnoid villi and the bridging veins act as potential paths of communication. Our low proportion (2 per cent) of cases of complicating subdural suppuration seems to indicate that the arachnoid membrane

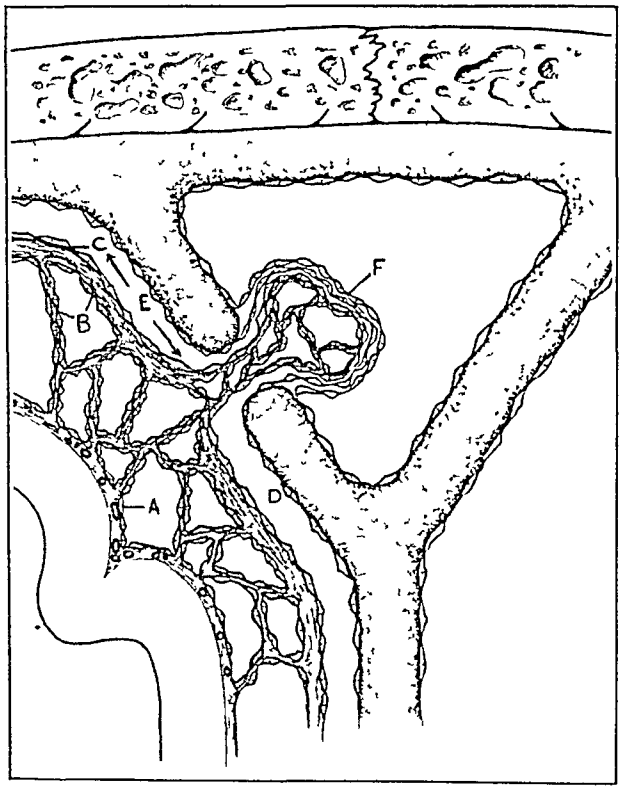

Fig. 5.—Diagrammatic representation of the layers of the meninges. *A*, outer layer of pia (incomplete layer of mesothelial cells); *B*, inner layer of arachnoid (incomplete layer of mesothelial cells); *C*, outer layer of arachnoid (complete layer of mesothelial cells); *D*, inner layer of dura (complete layer of mesothelial cells); *E*, subdural space, and *F*, arachnoid villus.

is an effective barrier to the spread of infection, despite its tenuous nature.

From a study of our autopsy material, we have derived several methods of possible spread from the subarachnoid space into the subdural space.

The first, and most obvious, mechanism is that of direct extension through the arachnoid membrane (fig. 2). This may occur in cases of chronic leptomeningitis or of leptomeningitis caused by organisms with unusual cytolytic powers. In none of our cases was the infection due to the meningococcus, the most common cause of leptomeningitis.

The second possible method of extension into the subdural space is through the medium of the arachnoid villi (fig. 3 *A* and *B*). Bateman[1] claimed that the villi are involved in every case of leptomeningitis. This is to be expected, since the villi are simply protruding extensions of the subarachnoid space. As the result of massive involvement of the arachnoid villi, necrosis of the boundary membranes may occur, permitting the escape of infected contents into the subdural space. With less severe involvement of the villi, the selective permeability of the membrane may simply be disturbed enough to permit the passage of bacteria, without actual destruction of the membrane barrier. Bateman showed that infection of the subdural space immediately adjacent to the arachnoid villus is not unusual. In our own experience, in most cases of purulent leptomeningitis the arachnoid villi show massive involvement, although gross extension into the subdural space has been seen only rarely.

A third possible mechanism of extension is involvement of the bridging veins (fig. 5). These veins traverse both the subarachnoid and the subdural spaces and, because of their incomplete covering of mesothelium, may readily be infected with purulent leptomeningitis.[3] Once there are involvement of the vessel wall and a resultant septic thrombus, the infected contents may be transmitted into the subdural space through necrosis of the vessel wall.

Another possible method of extension, which we have not seen, consists of thrombophlebitis of the bridging veins, resulting in secondary thrombosis of the sinus with retrograde involvement of the subdural space over the pacchionian granulations.

The fifth possible mechanism of extension is the inoculation of both the arachnoid and the dura by a blood-borne infection, with simultaneous involvement of both membranes. We have never seen this occur and mention it only for completeness.

We have purposely omitted from consideration the obvious artificial contamination of the subdural space resulting from spinal or cisternal puncture. In our first case no subarachnoid drainage whatever was performed. In the second case there was subdural infection over the dorsum of the brain, with no infection in the region of the puncture. The latter condition eliminated the possibility of artificial contamination.

3. Courville, C. B.: Subdural Empyema Secondary to Purulent Frontal Sinusitis, Arch. Otolaryng. **39**: 211-230 (March) 1944.

CLINICAL APPLICATION

The occurrence of subdural infection is clinically important both as a serious immediate complication of leptomeningitis and as a possible cause of postmeningitic epilepsy at some future date. It is well known that epilepsy is not an uncommon sequel to meningitis following otitis media, particularly when the meningitis is caused by a pneumococcus, a streptococcus or a staphylococcus. However, epilepsy is a most unusual complication of the ordinary meningococcic meningitis. This may be due to the fact that subdural empyema is a not infrequent complication of meningitis caused by a gram-positive coccus, but rarely follows meningococcic meningitis. Ney [4] showed conclusively that the presence of scar tissue between the dura, the arachnoid and the brain tissue produces traction on the brain, as a result of the dura's inelasticity and rather firm fixation to the skull. He stated the theory that the area of cortex on which traction is exerted gradually becomes increasingly irritable, eventually constituting an epileptogenous zone. These adhesions can be demonstrated by roentgenographic technics developed by Ney. Confirmatory proof of the causal relation of these adhesions to the occurrence of epilepsy has been obtained at operation by tugging on the adhesion and initiating an epileptiform seizure. In contrast to the occasional dramatic symptoms produced by adhesions between the dura, the arachnoid and the cortex, the adhesions between the arachnoid and the brain substance alone are of little apparent significance. Such adhesions are frequently a purely incidental observation at autopsy in cases with no history of convulsions.

In view of its serious consequences, therefore, it is important to bear in mind the possible occurrence of subdural empyema, particularly in chronic purulent leptomeningitis or in the leptomeningitides caused by the gram-positive cocci or by H. influenzae. Diagnosis must be made early. Courville [3] discussed the symptoms in some detail. Conspicuous features of subdural extension are severe persistent headache and general signs of sepsis out of proportion to the localizing signs. No program of treatment has yet been applied; however, it is suggested that penicillin with surgical drainage may prove of value. The existence of this lesion has an important bearing on the prognosis of leptomeningitis, both because it acts as a seeding focus for sepsis and because it may produce pressure atrophy of the cortex. Its possible occurrence should be kept in mind.

CONCLUSIONS

1. Subdural suppuration appears as a rare complication of purulent leptomeningitis, although a higher incidence will undoubtedly be revealed as a result of more complete autopsy studies.

2. Several possible mechanisms of the spread of infection from the subarachnoid to the subdural space exist.

3. This condition has significance both as an immediate serious complication and as a possible cause of postmeningitic epilepsy.

4. It is noteworthy that this complication did not occur with meningococcic infection, the most common cause of leptomeningitis.

4. Ney, K. W.: Pathologic Factors in the Production of Traumatic Epilepsy, J. M. Soc. New Jersey **40**: 270-275, 1943.

HYPERTHERMIA FOLLOWING INJURY OF THE PREOPTIC REGION

REPORT OF A CASE

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AND
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Acute cerebrogenic hyperthermia has long been recognized as an entity of neurosurgical importance (Cushing,[1] Gagel,[2] Dott,[3] Erickson,[4] Davison [5] and Zimmerman [6]). Clinical accounts have indicated that this type of high, and often fatal, fever is caused by injury of the hypothalamus or of nearby parts of the brain, a general conclusion in accord with the results of recent animal experimentation. However, in most instances of neurogenic hyperthermia in man the cerebral damage has been diffuse, and localization of the responsible region has not been as precise as that achieved by special technics in animals. The most discrete lesions described in the literature are those presented by Alpers.[7]

The following case is thought worthy of record because the injury of the brain that was believed to have destroyed central mechanisms for heat loss and thus have resulted in the extreme elevation of body temperature was more circumscribed than the lesion noted in any other report with which we are acquainted.

1. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. Gagel, O.: Symptomatologie der Erkrankungen des Hypothalamus, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, pp. 482-522.

3. Dott, N. M.: Surgical Aspects of the Hypothalamus, in Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus, London, Oliver & Boyd, Ltd., 1938, pp. 131-185.

4. Erickson, T. C.: Neurogenic Hyperthermia (A Clinical Syndrome and Its Treatment), Brain **62**:172-190, 1939.

5. Davison, C.: Disturbances of Temperature Regulation in Man, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:774-823, 1940.

6. Zimmerman, H. M.: Temperature Disturbances and the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:824-840, 1940.

7. Alpers, B. J.: Hyperthermia Due to Lesions in the Hypothalamus, Arch. Neurol. & Psychiat. **35**:30-42 (Jan.) 1936.

REPORT OF CASE

History.—A white infantry soldier, appearing to be in his early thirties, was brought to an evacuation hospital in a forward zone on March 17, 1944, at 9:50 a. m. He had been struck by a mortar shell fragment, which had inflicted a lacerated gutter wound of the right temple. Because of severe combat conditions no associates could be reached for a detailed account of the way in which the injury was incurred. From the ambulance driver it could only be learned that the patient had been hit thirty to sixty minutes prior to the time of admission, that he had become immediately unconscious and that he had been given ½ grain (0.032 Gm.) of morphine sulfate hypodermically.

He had been taken to the shock ward and had received 1 unit of plasma before he was examined.

Examination.—The patient was in coma and did not react to painful stimulation. He was well nourished and well developed, and physical examination revealed no abnormalities except the wound in the head. The oral temperature was 98.6 F., the pulse rate 80 and the respiratory rate 16 per minute, and the blood pressure was 120 systolic and 60 diastolic. A 4 inch (10 cm.) gash extended horizontally across the right temple. Torn muscle was exposed. Neurologic examination demonstrated active and bilaterally equal deep reflexes and brisk superficial reflexes. The Babinski toe sign was elicited in each foot. There was no papilledema. The pupils were fixed at 2.5 mm. An emergency roentgenogram of the skull disclosed no evident fracture.

Course of Illness.—With the use of local infiltration with procaine, the scalp and temporal muscle were debrided, and the wound was closed. At noon, when the patient was next visited, his oral temperature had risen to 100 F. He had become completely vegetative, and no reflex responses could be obtained. The pulse rate was 100 and the respiratory rate 6 to 8 per minute, with periods of apnea. The pupils were still fixed at 2.5 mm. By 3 p. m. the breathing was further slowed and more irregular, and the oral temperature had reached 106.4 F. The pupils were unchanged. An unsuccessful attempt had been made to reduce the fever by sponging with cold water.

After a review of the history to this point, a diagnosis of cerebral laceration with subdural hematoma was made. As soon as an operating table was free, he was taken to the surgical tent. At 6 p. m. an osteoplastic craniotomy was done in the right temporal region. An extensive epidural hemorrhage was encountered, and incision of the dura mater revealed a fresh, massive temporoparietal subdural hematoma. When the latter was removed by suction, the under-

lying cortex was seen to be covered with widespread subpial hemorrhage. As an attempt was being made to control the bleeding from the middle meningeal artery, the patient suddenly stopped breathing and shortly died, in spite of artificial respiration. A few moments before death respiration had seemed more regular. The terminal rectal temperature was 108.2 F.

Necropsy.—Postmortem examination, which was made at once, revealed no pathologic changes except those of the skull and its contents. Two roughly vertical, linear breaks of the right temporal squama, crossing the squamosal suture into the inferior portion of the parietal bone, were discovered. (On reexamination of the roentgenograms one of these fractures could be made out.) The more anterior of the fractures connected with a fracture line which ran over the petrosal part of the temporal bone, traversing the arcuate eminence and ending over the internal acoustic meatus. The middle meningeal artery was torn in a wing of this crack, which ran toward the foramen spinosum.

Inspection of the brain showed extensive contusion and slight laceration on both sides of the right lateral cerebral fissure and an area, oval and 2 inches long, of more severe cortical laceration of the right middle temporal gyrus. After removal of the hemispheres it was seen that the dura mater lining the right middle cranial fossa was finely streaked with blood, as though the dura mater itself was bruised. This was most pronounced anteriorly, on the cerebral face of the greater wing of the sphenoid bone.

The brain was sectioned immediately, since no facilities for preservation were available. No ventricular hemorrhage was present. There was no damage to the brain stem except for slight softening of the central gray matter of the mesencephalon at the level of the inferior colliculus. In the left hemisphere a long, stablike hemorrhage ran through the caudate nucleus and into the upper part of the internal capsule, from a frontal level of the anterior commissure to a frontal level of the middle of the thalamus. There was no other injury of the basal ganglia.

The only other lesion, and the one which seemed most significant, was a localized softening of the preoptic region, on both sides of the optic recess of the third ventricle, between the optic chiasm and the anterior commissure. This area did not widen as far laterally as the globus pallidus at any point. Posteriorly it was sharply delimited and did not involve the tuberal portion of the hypothalamus. Anteriorly it extended to the limit of the preoptic substance.

COMMENT

This case by no means presents final evidence that the division of the brain principally damaged, the preoptic area, is the center containing neural mechanisms for control of heat loss in man, destruction of which results in neurogenic hyperthermia. First, unfortunately, the patient was seen in a battle situation which precluded adequate investigation of the brain. It is possible that microscopic study of prepared material would have disclosed other pathologic changes. Second, the patient was wounded and treated in a tropical theater of war, and high environmental temperature may have played a role in the development of his fever. However, the temperature on the day of his hospitalization was in the middle eighties, and we do not believe it was a factor. No case of hyperthermia was noted among many other men with severe head injuries who were cared for under the same climatic conditions. Third, epidural and subdural hemorrhage produced general encephalic compression, and other areas of cerebral damage of the midbrain, the caudate nucleus, the internal capsule and the temporal and frontal cortex, existed. Yet none of these regions, or any combination of them, has to our knowledge, ever been implicated as an anatomic factor in the production of cerebrogenic fever.

Perhaps an attempt should have been made to reduce the fever with pentobarbital sodium, as suggesaed by Beaton, Leininger, McKinley, Magoun and Ranson,[8] or with other drugs (Erickson[4]). The extreme embarrassment of respiration was the factor which decided us against pharmacologic intervention. If operation had been successful and respiration had improved, administration of pentobarbital sodium would have been tried.

The particular interest of this case lies in the localization of the lesion presumably accounting for the elevated temperature to a small part of the brain, the preoptic region. In the monkey, local heating of this area with high frequency currents results in the activation of mechanisms for heat loss (Beaton, McKinley, Berry and Ranson[9]), while circumscribed destruction of the area causes central paralysis of these processes and consequent fatal hyperthermia (Beaton, Leininger, McKinley, Magoun and Ranson[8]). In spite of the limitations on pathologic study imposed by the conditions under which the case was observed, the results seem to lend credence to the supposition that in man, also, the site of central mechanisms for heat loss is the preoptic region.

SUMMARY

A case of injury of the preoptic region with subsequent development of neurogenic hyperthermia presents evidence that this area contains the specific neural mechanisms for heat loss in man.

8. Beaton, L. E.; Leininger, C.; McKinley, W. A.; Magoun, H. W., and Ranson, S. W.: Neurogenic Hyperthermia and Its Treatment with Soluble Pentobarbital in the Monkey, Arch. Neurol. & Psychiat. **49**:518-536 (April) 1943.

9. Beaton, L. E.; McKinley, W. A.; Berry, C. M., and Ranson, S. W.: Localization of Cerebral Center Activating Heat-Loss Mechanisms in Monkeys, J. Neurophysiol. **4**:478-485, 1941.

Minor Notes

DETECTION OF LATENT EXTENSOR PLANTAR REFLEX

ALFRED GORDON, M.D., PHILADELPHIA

Margolis and Graves [1] have described a method to facilitate the detection of the latent Babinski sign. Injection of a strong dose of scopolamine hydrobromide produces the desired reflex when there is doubt as to the organic nature of the condition in a given case. The authors' investigations cover a sufficiently large number of patients to justify them in the assumption that in "none of the aforementioned patients did a latent Babinski sign appear in the absence of damage to the pyramidal tract." They cite a number of authors who used this test to bring out a latent pyramidal sign, although the majority experimented only in cases of parkinsonism. The latter disease is, of course, essentially a pathologic condition of the extrapyramidal system. Nearly all authors have claimed that the pyramidal involvement is only a subsequent complication and that when the plantar reflex is evoked in extension with scopolamine there must be involvement of the pyramidal system. .

Special attention is called to Link's work on induction of narcosis in mentally deranged patients, to whom scopolamine was invariably given with morphine. The question arises which of the two drugs was responsible for evoking an extensor plantar reflex or perhaps whether both could be incriminated. Volkmann observed the extensor plantar reflex in patients anesthetized with scopolamine and morphine for surgical operations. Zador obtained the reflex response not only in patients with postencephalitic parkinsonism but in normal persons who were given scopolamine in doses over 1 mg.

1. Margolis, L. H., and Graves, R. W.: Detection of the Latent Babinski Sign with Scopolamine, Arch. Neurol. & Psychiat. **52**:409 (Nov.) 1944.

At this juncture I refer the reader to a previous communication.[2] Briefly, a middle-aged man with a normal nervous system received from a pharmacist a potion containing morphine for relief from an attack of his usual rheumatism. The amount of morphine sulfate was a little over 1 grain (0.065 Gm.). Half an hour later he became comatose. When he regained consciousness, he noticed he could not walk easily. On examination at the Jefferson Hospital, I observed a typical picture of spastic paraplegia, with a notably increased patellar reflex, ankle clonus and extensor plantar reflex. Seventeen hours later all the symptoms of lateral sclerosis disappeared. It is evident that degeneration of the motor tract is not necessary to produce the aforementioned symptoms. One is forced to infer that irritation or functional disturbance from any cause is sufficient to evoke pathologic phenomena referable to the motor tract.

In the case just described toxicity (morphine poisoning) probably produced the irritation of the pyramidal tract in the spinal cord. In cases of epileptic coma (not of jacksonian type) I have frequently observed an extensor plantar reflex, which disappeared on recovery from the coma. In cases of chronic alcoholism the presence of an extensor plantar reflex is probably due at first to the toxic effect of alcohol on the motor cortex and later, by reason of chronicity, to secondary organic changes.

There is no doubt that the scopolamine test is a valuable aid in detection of organic changes in the pyramidal tract in doubtful cases, but an extensor plantar reflex may be elicited also in persons with a normal nervous system when it is exposed to irritating toxic elements.

2. Gordon, A.: Spinal Symptoms Caused by Acute Morphine Poisoning, Philadelphia M. J. **11**:497 (March 21) 1903.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

UTILIZATION OF OXYGEN BY THE BRAIN IN TRAUMATIC SHOCK. A. BLALOCK, Arch. Surg. **49**:167 (Sept.) 1944.

In anesthetized dogs shock was produced by hemorrhage, trauma, burns and tourniquets, and the oxygen contents of the blood obtained from the femoral artery, the right auricle and the cerebral venous sinuses were determined. In the state of shock there was usually an increase in the difference between the oxygen content of arterial and that of cerebral venous blood even before the blood pressure began to drop. Under conditions of decreasing blood flow the brain, unlike the kidneys, appears to maintain its oxygen consumption, at least partially, by extracting increased amounts of oxygen from the arterial blood.

LIST, Ann Arbor, Mich.

NON-PROTEIN NITROGEN AND PROTEIN CONCENTRATIONS OF SERUM AND CEREBROSPINAL FLUID IN SHOCK. GEORGE W. DUNCAN, J. LOGAN IRVIN and STANLEY J. SARNOFF, Bull. Johns Hopkins Hosp. **75**:135 (Aug.) 1944.

Duncan, Irvin and Sarnoff report observations on the nonprotein nitrogen and protein concentrations of the serum and the cerebrospinal fluid in dogs subjected to experimental shock produced by a crushing injury to a limb. These observations were compared statistically with data obtained from a control group of dogs.

The authors observed that the mean concentrations of both nonprotein nitrogen and protein in the serum and the cerebrospinal fluid were significantly greater for the animals subjected to trauma. The mean ratios of the concentrations of nonprotein nitrogen in the serum to the corresponding concentration in the spinal fluid were 1.58 for the controls and 2.02 for the animals in shock. The mean ratios of the concentration of protein in the serum to the corresponding concentration in the cerebrospinal fluid were essentially the same for the two groups. These experiments indicate that if alteration in the barrier relation between plasma and cerebrospinal fluid does occur in shock produced by this method, it is not sufficient to permit extensive passage of plasma protein into the spinal fluid.

GUTTMAN, Philadelphia.

INTERACTION OF NEIGHBORING FIBERS IN MYELINATED NERVE. AMADEO S. MARRAZZI and RAFAEL LORENTE DE NÓ, J. Neurophysiol. **7**:83 (March) 1944.

Marrazzi and Lorente de Nó studied the sciatic nerve of the bullfrog to determine the changes in excitability of the fibers of the medial peroneal nerve after the administration of a two-thirds maximal shock to the lateral peroneal nerve. The results of the experiments were expressed in the form of interaction curves, the interaction being due to the flow of action currents of the active fibers through the membrane of the inactive fibers. The interaction current could be differentiated into two parts: an immediate and a residual interaction current, the latter outlasting the flow of the action currents. The residual interaction current had an electric sign consisting of a change in membrane potential. The shape of the interaction curve depends on the geometric conditions determining the low of the action current through the inactive fibers and on the temporal course of the stimulating fibers.

FORSTER, Philadelphia.

THE ELECTRICAL ACTIVITY OF REGENERATING NERVES IN THE CAT. CHARLES M. BERRY, HARRY GRUNDFEST and JOSEPH C. HINSEY, J. Neurophysiol. **7**:103 (*March*) 1944.

Berry, Grundfest and Hinsey under sterile conditions divided and then sutured the sciatic nerves, or the tibial and peroneal branches, of 58 cats. Evidence of return of motor and sensory functions was observed. At periods varying up to four hundred and sixty-six days acute experiments were performed and the effects of stimulation in situ determined. After this the nerves were excised, and the electrical response to stimulation and the histologic state of the nerves were determined.

The authors observed the presence of small, slowly conducted action potentials as early as seventeen days after operation. As the postoperative time became longer the potentials increased in size, velocity and complexity. The threshold for stimulation of regenerating fibers was high peripherally and low centrally with reference to the suture. In the course of time the peripheral threshold decreased. As the impulse passed the suture an abrupt drop in velocity occurred. In the fibers distal to the suture the return of conduction velocities was slow, and the increase in velocity was at a constantly decreasing rate. The return of maximum fiber diameter took a similar course. The relation of maximum fiber diameter to maximum conduction velocity was linear.

FORSTER, Philadelphia.

RELATION OF THRESHOLD FOR EXPERIMENTAL CONVULSIONS TO BODY WEIGHT. FEDERICO SAL Y ROSAS, Rev. neurol. de Buenos Aires **8**:302 (July-Sept.) 1943.

The relation of the minimum amount of metrazol necessary to cause a convulsion to body weight was studied in 204 subjects, 107 of whom were epileptic. On the whole, the convulsive threshold varied directly with the weight of the patient. The author emphasizes the significance of other factors, such as a history of epilepsy, a tendency to hysterical convulsions and the use of sedatives. The mean minimal dose for all patients who had been without phenobarbital for a long time was 5.5 mg. per kilogram of body weight, 4 mg. for epileptic patients and 6.3 mg. for nonepileptic patients. The minimal dose per kilogram of body weight is less for patients with conversion hysteria with a history of convulsive movements than for hysterical patients without such a history.

SAVITSKY, New York.

Neuropathology

CYSTICERCUS CELLULOSAE OF THE BRAIN. META A. NEUMAN, J. Neuropath. & Exper. Neurol. **2**:197 (April) 1943.

The case reported is that of an American aged 35, returned from the Orient, who had been hospitalized

in the United States for eight years and was suspected of having dementia paralytica. He had had the first convulsion nine years before death. In spite of intensive antisyphilitic therapy, he grew worse, and his convulsions became more frequent and severe. Neurologic examination suggested diffuse, chronic encephalomeningomyelitis. He finally died, with a a temperature of 108 F. Autopsy revealed numerous cysticerci scattered throughout the brain. As well as could be determined, the patient had never harbored an intestinal parasite.

Cerebral cysticercosis should be considered in the cases of adults who have lived in foreign countries and who have their initial convulsions relatively late in life.

CAMPBELL, New York.

NEUROHISTOLOGIC FINDINGS IN EXPERIMENTAL ELECTRIC SHOCK TREATMENT. N. W. WINKELMAN and MATTHEW T. MOORE, J. Neuropath. & Exper. Neurol. **3**:199 (July) 1944.

Winkelman and Moore report their observations in a study of 12 cats. One group, of 8 animals, was treated with the faradic shock modality used by Berkwitz, while the other group, of 4 animals, was treated with the modality advocated by Cerletti and Bini, using the Offner machine. Treatments were given three times a week. Most of the animals received a series of from ten to twenty shock treatments before they were killed. The nutrition of the animals was carefully controlled. The cats were killed by being bled while under ether anesthesia three days to ten weeks after the last treatment. The brain and cord of all the animals were removed immediately, fixed in a 4 per cent concentration of solution of formaldehyde U. S. P. for twenty-four hours and then cut and placed in alcohol. Sections were embedded in paraffin and pyroxylin, and frozen sections were made. The sections were stained with hematoxylin and eosin, toluidine blue, Weil's stain for myelin sheaths, Bodian's stain and scarlet red, while the Cajal and Hortega technics were employed for the various types of glia.

Histologic studies of the brain and cord of all the animals were made, many by serial sections. No morphologic changes were observed in animals receiving convulsive doses of electric current analogous to those given to patients. Two animals received excessive doses of electric shock. The brain of 1 of these cats showed a small area of pericapillary hemorrhage, while in the other some of the smaller blood vessels were congested. No instance of subarachnoid hemorrhage or diffuse or extensive intracerebral hemorrhages was noted.

Winkelman and Moore believe that when hemorrhages occur in the brain of an animal after electric shock convulsion one or more of the following factors were operative: (1) The intensity of the current was excessive as compared with the corresponding dose used with human subjects; (2) deprivation of vitamin B and C, and probably vitamin K, occurred during the course of treatment, and, finally, (3) craniocerebral injury, due to inadequate restraint and protection, was incurred during the convulsion.

GUTTMAN, Philadelphia.

THE PATHOLOGICAL CHARACTERISTICS OF EMBOLIC OR METASTATIC ENCEPHALITIS. BERNARD J. ALPERS and HERBERT S. GASKILL, J. Neuropath. & Exper. Neurol. **3**:210 (July) 1944.

Alpers and Gaskill report their observations in 17 cases of embolic encephalitis. Attention was focused on changes in the brain and the source of the embolic foci. The material was obtained from cases representing the following sources of the emboli: subacute bacterial endocarditis, 5 cases; acute vegetative endocarditis, 5 cases; bronchiectasis, 3 cases; pulmonary abscess, 1 case; gangrene of the foot, 1 case; retroesophageal abscess, 1 case, and osteomyelitis of the hip, 1 case. Sections were taken from all parts of the cerebral hemispheres, the brain stem and the cerebellum and were embedded in paraffin and pyroxylin. In many instances studies by serial section were made in order to study the origin and development of the encephalitic foci. Hematoxylin and eosin, toluidine blue, Weil's stain for myelin sheaths, Cajal's gold chloride stain for astrocytes, scarlet red for fat and, in some instances, Bodian's stain for axis-cylinders were employed.

The authors state that the commonest cause of metastatic encephalitis is bacterial endocarditis, particularly of the subacute variety. Acute endocarditis, pulmonary disease and infections of other organs may give rise to this type of encephalitis. The clinical manifestations indicating involvement of the brain, particularly in cases of endocarditis, may usher in the disease; they may be terminal or may occur at any time during the course of the illness.

The number of areas of encephalitis vary from a few to many. They occur in the cerebral hemispheres, the brain stem and the basal ganglia. Microscopic study reveals proliferative endarteritis, which tends to be generalized; areas of perivascular infiltration with leukocytes; minute leukocytic nodules, which are essentially miliary abscesses, and, in some instances, areas of petechial and perivascular hemorrhage. Subarachnoid, cerebral or ventricular hemorrhage may be seen, as well as meningitis.

Alpers and Gaskill conclude that metastatic encephalitis is probably due to blood-borne bacteria, which are probably disseminated by the system of paravertebral veins described by Batson.

GUTTMAN, Philadelphia.

ALTERATIONS IN BRAIN STRUCTURE AFTER ASPHYXIATION AT BIRTH: AN EXPERIMENTAL STUDY IN THE GUINEA PIG. W. F. WINDLE, R. F. BECKER and ARTHUR WEIL, J. Neuropath. & Exper. Neurol. **3**: 224 (July) 1944.

Windle, Becker and Weil report observations on the effect of asphyxia in guinea pigs. Proof that asphyxia leads to neurologic defects may never be found in the human newborn infant because adequately controlled conditions—multiple births—are uncommon. These animal experiments supplement clinical observations.

The experimental procedure in most instances was as follows: Pregnant guinea pigs at, or close to, term were operated on after the abdomen was anesthetized with a 1 per cent solution of procaine hydrochloride. One fetus of each litter was delivered without delay to serve as the control for the fetuses to be asphyxiated. The uterine blood vessels or the umbilical cord was then occluded with clamps to induce a state of hypoxia in the remaining fetuses. Violent movements, including respiratory activities in utero, were executed during the first stage of asphyxia. When their respiratory efforts ceased, the fetuses were delivered. The average duration of asphyxiation was a little over thirteen minutes (range, four and a half to twenty-one minutes). The average time required for resuscitation (with oxygen containing 10 per cent carbon dioxide) was twenty-

nine minutes (range, a few seconds to well over an hour) for the 66 animals selected for study. Some litters contained three or more animals, and two or more fetuses were asphyxiated; 50 controls were provided. Sixty-six of the newborn guinea pigs were resuscitated and lived thirty minutes to thirteen weeks. The brains of all the animals were preserved and sectioned serially. Observations were made on sections stained by various technics.

Multiple capillary hemorrhages, and occasionally larger hemorrhages, were noted in all animals which survived asphyxiation for three hours to five days. These lesions were observed in half the animals which survived from thirty minutes to two hours, while no lesions were observed in the animals which did not survive the period of asphyxia. There was a notable variation in the amount and distribution of the hemorrhages. However, hemorrhage was not considered the cause of extensive damage to the neurons.

Edema was present in the brains of all but 1 of the animals which survived eight hours to four days after resuscitation. After five days the edema subsided.

Cytologic changes were observed in all the brains of animals killed from one and one-half hours to twenty-one days after resuscitation. The usual sequence of events was clouding of the Nissl granule pattern, beginning one to two hours after resuscitation; swelling of some neurons and shrinkage of others in three hours; loss of stainability with thionin, appearing in about five hours; typical chromatolysis, in one or two days, complete lysis of neurons as early as four days after resuscitation and hyperchromatic staining in at least three weeks. Some specimens presented generalized changes throughout most of the brain, while others showed only focal abnormalities. The cerebellum and the corpus striatum were not notably affected, while the thalamus, cerebral cortex, tegmentum and spinal cord were often severely damaged.

Asphyxia induced a transient microglial reaction between two days and three weeks after resuscitation. Thereafter the glia assumed normal proportions.

Generalized or focal atrophy followed the loss of neurons in about two thirds of the severely asphyxiated animals and in one half of the mildly asphyxiated guinea pigs. As late as thirteen weeks after resuscitation neurons in the damaged brains stained darker and were more shrunken than the neurons in the brains of litter mate controls. Areas of partial necrosis occurred in 8 animals. Loss of myelin appeared to be secondary to loss of cells.

The authors conclude that experimental asphyxiation followed by successful resuscitation in guinea pigs at birth produced pathologic changes of variable degrees of severity in all specimens of the brain studied between one and one-half hours and three weeks after birth and detectable permanent anatomic changes in more than one-half the animals allowed to live more than three weeks.

GUTTMAN, Philadelphia.

A CASE OF ATYPICAL LINDAU'S DISEASE. W. R. BRAIN, J. G. GREENFIELD and D. W. C. NORTHFIELD, J. Neurol. & Psychiat. **6**:32 (Jan.-April) 1943

Brain and his associates report an unusual case of Lindau's disease without the presence of cerebellar tumor. The findings were a hemangioblastoma in one retina and two similar lesions in the other, a hemangioblastoma of the spinal cord associated with extensive syringomyelia and cysts of the pancreas and kidneys. There was evidence of hereditary transmission of the disease. According to most statistics, hemangioblastoma is more common as a primary tumor in the cerebellum than in the spinal cord, the cauda equina or the cerebral hemispheres. The syringomyelia was interpreted as a separate developmental anomaly.

MALAMUD, Ann Arbor, Mich.

Psychiatry and Psychopathology

PSYCHONEUROLOGICAL PROBLEMS RELATED TO THE SURGICAL TRANSSECTION OF THE PREFRONTAL ASSOCIATION AREAS IN MAN. GEORGE W. KISKER, J. Nerv. & Ment. Dis. **99**:343 (April) 1944.

The operation of prefrontal lobotomy or leukotomy provides a unique opportunity to study the behavioral changes in a large number of subjects after the production of a relatively exact lesion. Twenty patients on whom the operation had been carried out were studied by the author from the viewpoint of the relations existing between the prefrontal association areas and the diencephalon and the autonomic representation in the cortex.

On the basis of retrograde degeneration after cortical ablations, Walker concluded that the thalamus can conveniently be divided into three nuclear groups: The first group has exclusively subcortical connections; the second receives fibers from the ascending sensory tracts and sends efferent fibers to the cortical projection areas, and the third receives no ascending fibers but makes numerous connections with the thalamic nuclei of the second group and projects to the cortical associative areas. The thalamus is viewed as a subcortical center where incoming impulses are integrated to some degree.

There is considerable evidence for autonomic representation in the frontal cortex, the cortical influence being primarily inhibitory. Thus, section of the frontal lobes should decrease autonomic inhibition; the validity of this assumption was borne out by the behavioral changes in the patients, who displayed increased hunger, sphincter disturbances, dysfunction of the temperature control mechanism, nausea and vomiting, decreased anxiety and tension and somnolence. The last symptom is especially interesting in view of the great weight of evidence in favor of a center for waking and sleeping in the hypothalamus and the demonstrated neural pathways connecting the frontal poles and the hypothalamic complex.

The therapeutic effect of the operation may be due to interruption of the corticothalamic tracts and the consequent modification of affectointellectual relations. It is well established that there are direct tracts connecting the prefrontal lobe with the medial thalamic nuclei. These fibers make up the anterior thalamic radiation and bear the brunt of the damage in lobotomy. However, the cerebropontile connections from the frontal lobes to the nuclei of the pons are also probably affected, and there are tracts indirectly connecting the frontal lobes and the cerebellum. It is thus possible to visualize an intellectual-affective-motor chain which includes the prefrontal association areas, the medial thalamic nuclei, the cerebellum, the pons and tracts returning once again to the frontal lobes. The disruption of this chain by lobotomy leads to interference with affective patternization and to a concomitant

restructuralization of the motorium, which accounts for the therapeutic effects of the procedure.

CHODOFF, Langley Field, Va.

BIOCHEMICAL COMPONENT OF THE MANIC DEPRESSIVE PSYCHOSIS. PERRY C. BAIRD, J. Nerv. & Ment. Dis. **99**:359 (April) 1944.

The manic phase of manic-depressive psychoses has been considered to have some relation to overfunction of the adrenal gland. To investigate this concept, Baird injected whole blood from manic patients into adrenalectomized cats and compared these animals with respect to behavior and duration of life with a group of control adrenalectomized animals which received whole blood from normal subjects. The average duration of life following adrenalectomy in the cats receiving blood from the manic patients was eleven and a half days for 4 cats and ten and one-third days for 7 cats. In contrast, the 7 control cats receiving normal blood lived an average of four days. It was observed that 2 of the adrenalectomized cats receiving blood from manic patients displayed unusual strength and endurance, and 1 of them exhibited dramatic rage reactions despite the absence of adrenal glands. Two adrenalectomized rats receiving blood from manic patients lived eight times as long as 3 adrenalectomized rats receiving whole blood from normal persons. In one experiment a transfusion of 500 cc. of citrated whole blood from a manic patient had no effect on a patient in a deep depression.

The author suggests that the manic psychosis may be due to overstimulation of the entire autonomic nervous system, with consequent increase in the nerve impulses to the anterior lobe of the pituitary gland, from which a reservoir of hormones break loose. These enter the circulation and bring about a tremendous increase in the secretions of the thyroid, adrenals and gonads, which, in turn, are responsible for many of the symptoms of the manic state, such as excessive sexual drive and quick recovery from fatigue.

CHODOFF, Langley Field, Va.

REFERRED HEAD PAIN AND ITS CONCOMITANTS. DOUGLAS G. CAMPBELL and CLARE M. PARSONS, J. Nerv. & Ment. Dis. **99**:544 (May) 1944.

In order to investigate the nature and varieties of referred head pain, the mesodermal structures of the cervical and basioccipital somites of a number of volunteer subjects were irritated by scratching the periosteum and periarticular structures with a fine needle or by the injection of 6 per cent sodium chloride in sterile solution. It was found that irritation of structures in the region of the occipitoatlantal condyle and the first cervical interspace posteriorly caused referred pain, which was predominantly orbital and frontal from the condylar or basal region and predominantly occipital from the nuchal tissues. Pain originating from the cervical interspinous ligaments (second to fifth) was predominantly occipital and upper cervical, with only occasional frontal reference. Concomitants of giddiness, pallor, sweating and nausea were seen with basal, suboccipital and interspinous irritation. These symptoms varied in intensity, extent and duration. Infiltration of trigger spots with procaine was uniformly successful in temporarily relieving heterotopic pain and usually ameliorated the concomitant symptoms. The resemblance of the subjective states produced to the post-traumatic "head" syndrome and to certain "neuralgias" and "myalgias" of the occipitocervical region was notable.

The type of pain produced in these experiments is referred to as sclerotomal, as differentiated from the dermatomal pain produced from somites below the fifth cervical segment.

The production of head pain from disease of the cervical, thoracic, and even lumbosacral, portions of the spine is explained as being due to hypertension of the long axial back muscles, with traction on their collagenous attachments to the occipital portion of the cranium.

Sensory impulses from the deep suboccipital muscles reach the upper two cervical segments of the spinal cord and here may become associated synaptically with the spinal tract and nucleus of the fifth nerve. This suggests a mechanism whereby irritation of the suboccipital structures can account for anterior head pain.

Also, the close functional interplay between the muscles of the eyes and the posterior cervical muscles provides an explanation for the equilibratory disturbances seen in cases of the post-traumatic syndrome in which deep nuchol pain and spasm of cervical muscles are prominent features. Muscle spasm, whatever its cause, can provide the starting point for a vicious cycle because the pain produced gives rise reflexly to further spasm. In patients suffering from tension and anxiety states the production of such a vicious cycle, with spasm of the cervical muscles leading to head pain and further spasm, is the probable mechanism of the headaches so frequently seen and described as functional.

CHODOFF, Langley Field, Va.

ON GENUINE EPILEPSY. RALPH R. GREENSON, Psychoanalyt. Quart. **13**:139, 1944.

Greenson believes that, in addition to a hereditary predisposition on an organic basis, a psychologic predisposition to genuine epilepsy exists. He presents data obtained from the partial analysis of a man aged 20 with epilepsy. The analysis revealed that the patient had strong aggressive, hostile and criminal drives, passive homosexual longings and exhibitionistic, scoptophilic impulses. These trends were present partly as reaction formations and partly as direct expressions of instinct. The patient had a strong tendency to accumulate tensions instead of discharging small quantities, to block motor outlets and to shift excitation to the central nervous system.

The aura was an anxiety equivalent and an orgasm derivative. In the seizures fantasies appeared containing castration ideas and allusions to incestuous wishes. Murderous, sadistic and destructive drives were fantasied in the preconvulsive and postconvulsive states.

The first attack was precipitated by a stimulus which was associated with infantile repressed material. Later attacks were precipitated by similar stimuli and by all situations which increased internal tensions—anxiety, sexual excitement or rage. The greatest obstacle in the analysis was the inability to analyze successfully the passive, homosexual aspects of the transference.

Greenson believes that the psychologic predisposition to genuine epilepsy consists in the presence of strong anal sadistic trends. All psychologic stimuli which increase internal tensions, especially those which touch on a repressed infantile nucleus, may precipitate an attack. The seizure itself is a trauma and is reacted to with phobic mechanisms. The attack also may be felt as a punishment. The seizures may permit the discharge of hitherto repressed fantasies.

The author believes that his case could be classified as one of pregenital conversion hysteria.

PEARSON, Philadelphia.

THE GUARDHOUSE INMATE, WITH A BRIEF DESCRIPTION OF THE "PSYCHOPATHIC PERSONALITY." WILLIAM ROTTERSMAN, War Med. **5**:271 (May) 1944.

Rottersman studied 50 unselected inmates of a post stockade, using the Harrower-Erickson multiple choice (Rorschach) test, the Shipley-Hartford Retreat test, a questionnaire covering information about the family history, age, education, length of service, conflicts with the law, childhood behavior disorders, psychotic trends and psychoneurotic complaints, sick call tendencies and breaches of military discipline and a personal interview. He found that approximately one third of the prisoners could be labeled pronounced psychopaths. The remaining two thirds were borderline psychopaths, persons of abnormal intelligence and persons with mental disease. Of the whole group, only 10 to 20 per cent could be considered normal.

The author believes that the majority of guardhouse prisoners should never have been inducted, but since they are in the service, they should not be returned to civilian life because of the harmful effect on the morale of the reliable, conscientious soldiers and their relatives. Some might be sent to "labor" battalions; some require institutionalization, and some might profit from psychotherapy or chemotherapy.

PEARSON, Philadelphia.

SUGGESTIBILITY AND HYSTERIA. H. J. EYSENCK, J. Neurol. & Psychiat. **6**:22 (Jan.-April) 1943.

Eysenck investigated the phenomenon of suggestibility in 60 subjects, 30 of whom were hysterical and 30 nonhysterical men and women. He used the progressive weights and lines tests, involving both personal ("prestige") and impersonal ("nonprestige") suggestion; the body sway test; the arm levitation test, and the Chevreul pendulum test, as well as tests for intelligence, perseveration and personal tempo. In none of the tests of suggestibility were there significant differences between the hysterical and the nonhysterical subjects or between men and women. Thus, although hysterical persons are suggestible, they are not more so than nonhysterical persons. The tests used involved two types of suggestibility—primary and secondary. Primary suggestibility was distributed in the experimental population in the shape of a U curve, showed high reliability, was correlated with intelligence in a nonlinear manner (i. e., subjects of average intelligence were the most suggestible) and was shown to involve a type factor dividing suggestibility into the active and the passive type. Secondary suggestibility was distributed in the shape of a normal curve, showed a low reliability and was correlated with intelligence in a linear manner; i. e., the more intelligent the subject, the less suggestible he was. Primary suggestibility seemed to be concerned with simpler tasks and was related to the phenomenon of dissociation, whereas secondary suggestibility dealt with more complex processes of judgment which would make dissociation difficult. Two factors of emotional response, viz., aptitude and attitude, were active in primary suggestibility. The personal tempo was negatively related to suggestibility, but perseveration did not show any definite relation to it.

MALAMUD, Ann Arbor, Mich.

Diseases of the Brain

MULTIPLE MENINGIOMAS. JOSEPH A. MUFSON and LEO M. DAVIDOFF, J. Neurosurg. **1**:43 (Jan.) 1944.

Multiple meningioma is so rare that in a series of 295 cases of intracranial meningioma (Cushing and Eisenhardt) there were only 3 instances of the condition. Likewise, it is only in rare cases that such multiple growths have been successfully removed. Mufson and Davidoff report the removal of multiple meningiomas in 2 cases.

In the first case ten meningiomas were removed in four successive operations over the course of three years. All the tumors were in the right hemicranium. Of interest is the notable transition in histologic form —from a benign psammomatous meningioma, obtained first, to a malignant tumor, removed at the last operation. In the second case two meningiomas of mixed type (benign) were removed at a single operation from the left hemicranium. In neither case were there any of the stigmas of Recklinghausen's disease.

WHITELEY, Philadelphia.

SPONTANEOUS VENTRICULAR RUPTURE IN HYDROCEPHALUS WITH SUBTENTORIAL CYST FORMATION. J. PENNYBACKER and D. S. RUSSELL, J. Neurol. & Psychiat. **6**:38 (Jan.-April) 1943.

Pennybacker and Russell report 2 cases of hydrocephalus resulting from obstruction of the aqueduct in which the dilatation of the lateral ventricles was accompanied by rupture of their walls in the region of the vestibule, producing a subtentorial cyst which communicated with the lateral ventricle. The site of rupture was that part of the ventricle wall which is thinnest normally, i. e., in the medial angle of the collateral trigone, between the forward-sweeping crus of the fornix and the forceps major. In a third case of hydrocephalus resulting from occlusion of the foramens in the fourth ventricle by adhesive arachnoiditis thinning occurred without rupture of this area of the wall of the lateral ventricle. Ventriculographic examination established the diagnosis. The treatment advocated by the authors is, first, the establishment of an opening in the anterior part of the third ventricle and, if this proves ineffective, a collapse of the cyst by the cerebellar approach.

MALAMUD, Ann Arbor, Mich.

Diseases of the Spinal Cord

TRAUMATIC SPINAL ARACHNOIDITIS: REPORT OF TWO CASES. LEOPOLDO SALAZAR VINIEGRA, Arch. de neurol. y psiquiat. de Mexico **6**:127 (March-April) 1943.

Salazar Viniegra reports 2 cases of injury to the back, 1 in a woman aged 38 and the other in a man aged 30. In both cases there were periods of freedom from complaints of two and six months respectively. In both cases the appearance of severe weakness and sensory changes in the lower limbs was rapid (two and four days respectively after onset of complaints). The passage of iodized poppyseed oil was stopped, but without the typical diffuse arrest of droplets. In 1 case only 1 cc. of spinal fluid was obtained, and in the other none could be withdrawn. There was an increase in cells and protein in the spinal fluid. No manometric studies are recorded. In 1 case the Kahn reaction of the blood was positive, a finding which the author considers coincidental. The diagnoses of leptomeningeal

adhesions in 1 case and of a meningeal cyst in the other were verified by operation. No histologic studies were reported. The author assumes a definite relation between the trauma to the back and the development of adhesive arachnoiditis. SAVITSKY, New York.

Peripheral and Cranial Nerves

PAIN REFERRED TO THE FACE, NECK, UPPER EXTREMITY AND CHEST DUE TO LESIONS IN THE EAR. HENRY P. SCHUGT, Arch. Otolaryng. **39**:430 (May) 1944.

Schugt reports 2 cases of chronic mastoiditis in adult women in which pain was referred to the face, neck, upper part of the arm and thorax. In the first case radical mastoidectomy had been done on the right side several years ago. At that time a cholesteatoma was observed in the mastoid antrum and middle ear, with extensive destruction of the bone, including the facial canal. Ten years later the wound began to discharge, after an infection of the upper respiratory tract. There was associated pain in the ear, and the patient was rehospitalized. Neurologic examination revealed nothing abnormal. A revision of the mastoid cavity revealed a small cholesteatoma near the opening of the eustachian tube. During the postoperative course it was observed that pain was initiated when the anterior wall of the mastoid cavity or when the eustachian tube was touched or packed with a thin tampon. The pain spread instantly over the entire auricle to the face, the eye, the temple, the upper and lower lip, the neck, the upper part of the arm and the upper and lateral part of the chest. The pain responded only to strong sedatives and to local applications of a 10 per cent solution of cocaine. A second revision of the mastoid cavity revealed no further pathologic process. The pain, however, recurred in the same manner as after the first revision. Gradually complete epithelization took place, and the pain subsided.

In the second case, pain developed in the ear, in the upper part of the arm and the upper part of the thorax. It was less violent than in the first case and was not felt below the fourth rib. There was no evidence of local tenderness in the arm or chest. After a modified radical mastoidectomy, the pain subsided and was not present during the postoperative period, as in the first case. The author points out that as the site of the lesion in the first case was within the distribution of the trigeminal nerve, the pain felt in the temple and face may be considered as referred pain, conforming with Head's theory. The same holds true for the pain in the upper cervical region and the upper part of the arm, as the trigeminospinal tract reaches the level of the upper cervical nerves. The thoracic pain is explained by the fact that impulses arising at the site of the lesion reach the upper thoracic segments of the spinal cord through afferent spinal nerve components which traverse the plexuses on the common and internal carotid arteries.

RYAN, Medical Corps, Army of the United States.

EROSION OF THE ALA NASI FOLLOWING TRIGEMINAL DENERVATION. J. SCHORSTEIN, J. Neurol. & Psychiat. **6**:46 (Jan.-April) 1943.

Schorstein draws attention to a new syndrome which he observed in 8 cases following trigeminal denervation either by section of the nerve or after injection of alcohol into the gasserian ganglion. In the resulting anesthetic area of the face erosion of the ala nasi occurred and was frequently associated with paresthesias, self-inflicted trauma, epistaxis, nasal fissures and facial ulcer. The author is of the opinion that erosion of the nostril results from self-inflicted injury in an attempt by the patient to relieve himself of paresthesia. A contributing factor is the diminished resistance of anesthetic skin to superimposed infection. The progression of the lesions may be determined by failure of the cutaneous vasodilator reflex. Treatment consists of warning the patients against manipulation of the skin and of covering ulcers and fissures with a bland ointment. MALAMUD, Ann Arbor, Mich.

Treatment, Neurosurgery

THE PICROTOXIN TREATMENT OF BARBITURATE POISONING. JOSEPH F. DORSEY, J. Nerv. & Ment. Dis. **99**: 367 (April) 1944.

Owing to the increasing use of the barbiturate drugs in suicidal attempts, the recognition and treatment of barbiturate poisoning has assumed considerable importance. In cases of severe intoxications, with coma impending or present, active, and at times heroic, treatment is required. The patient should be placed in shock position and gastric lavage instituted immediately. Specific treatment is based on the intravenous use of picrotoxin in an amount dependent on the depth of coma. The drug is injected at the rate of 1 cc. (3 mg.) per minute until the appearance of tremors of the extremities, twitching of the lips and eyelids and movements of the eyes. When this stage is reached, the frequency of administration of the dose is decreased to keep the patient at a level of minimal twitching, since at this point the cardiac and respiratory centers receive their maximal stimulation. Usually 1 cc. every five minutes is sufficient for this purpose, and with improvement this dose is gradually decreased. An overdose of picrotoxin may produce a convulsion. In addition to picrotoxin, application of heat, intravenous injection of fluids, administration of caffeine and sodium benzoate and, occasionally, inhalation of carbon dioxide and oxygen are indicated. If use of the picrotoxin is discontinued prematurely, the patient lapses again into deep coma.

CHODOFF, Langley Field, Va.

TREATMENT OF MENTAL DISEASE WITH ELECTRIC SHOCK. CESAR DELGADO, Rev. de neuro-psiquiat. **6**:263 (Sept.) 1943.

Electric shock therapy was used for the first time in Peru in January 1943. The author reports his results with 10 patients: 5 with schizophrenia, 2 with depressions, 1 with a manic state, 1 with a compulsive neurosis and 1 with psychoneurosis. Seven patients had complete remissions, and 3 showed notable improvement. There were no fractures. One patient incurred a readily reducible dislocation of the shoulder. All the patients with manic-depressive psychosis and 3 with schizophrenia had complete remissions. All the schizophrenic patients treated had been ill six months or less. No persistent mental sequelae were noted in any of the patients.

SAVITSKY, New York.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

Regular Meeting, March 10, 1944

Excessive Androgen in the Female. DR. MARGARET DE RONDE, Norristown, Pa.

Two interesting cases of pronounced virilism in females receiving androgen therapy were observed. Neither patient exhibited any indication of aberration in psychosexual development, although there was present enormous excess of androgens. In both patients the changes toward virilism, although substantial, were reversible.

DISCUSSION

DR. N. W. WINKELMAN: It is not pleasant to see the male characteristics produced in the female by excessive androgen therapy, especially when one has oneself prescribed the treatment. It is consoling that the condition is a reversible process, as has been stated this evening and as is recorded in the literature. My associates and I had been treating female psychiatric patients with androgen, and we had noted the growth of hair, the change of voice and the other alterations described. We, too, have observed reversibility. I must confess that the first time I saw such changes I was profoundly shocked, but the male characteristics eventually disappeared, after several months. Not more than 225 mg. of androgen per month per patient is recommended.

DR. HAROLD D. PALMER: One of the interesting facts brought out by Dr. De Ronde is the apparent absence in these patients of a relationship between psychosexuality and the endocrine state. In both her cases excess of androgen was continuous over a period sufficient to produce physical changes tending toward masculinity, and yet there was no parallel change in psychosexual interest. This observation becomes important with respect to the relation of hormone secretion and sexuality, not only with the normal, but in cases of sex variants. My associates and I, as well as other investigators, have shown that a high percentage of homosexual males excrete excesses of estrogen in the urine. It has been thought that administration of testosterone and other forms of androgen might conceivably inhibit the secretion of estrogen and might tend to produce a regression of feminine physical characteristics and a change toward normal psychosexuality. It seems to me that one will have to accept in part the concept that in some instances homosexuality is a neurosis, but that in others it is a psychobiologic entity and is, therefore, amenable to changes in the endocrine balance. I believe this theory would find a good deal of support in the glandular effects of treatment of homosexual males with large doses of testosterone. While we do not yet have any statistical statement to make, it has been our experience that in some cases normal psychosexuality develops after prolonged and intensive glandular therapy.

Psychiatric Experience on a Naval Hospital Ship. Lieut. R. S. WIGTON (MC), U.S.N.R.

Duty on a hospital ship combines the advantages of sea duty with those of working in a small, excellently equipped hospital unit and offers a varied and busy experience.

Of particular interest to the psychiatrist are the opportunities to see psychiatric battle casualties at an early stage, to compare the reactions of the men from varying types of duty and to be in close contact with wounded and medically ill men—caring for burns and treating medical or surgical casualties when conditions required.

In the care and transportation of the wounded and ill during the campaign at Guadalcanal, the high morale, patience and fortitude of these men were inspiring to see. During this campaign, 671 neuropsychiatric patients were handled, of whom 10 per cent were psychotic, slightly less than 50 per cent had the cardinal symptoms of "combat fatigue" and 25 per cent had various psychoneurotic reactions similar to those seen in civilian life.

The cruise of a year and a half provided an opportunity for observations on the reactions of the ship's crew to prolonged sea duty and to morale factors generally. A few of the original members of the crew, who had been out for over two years, presented reactions similar enough to constitute a syndrome, with symptoms of anorexia, insomnia, increased irritability and fears of their own impulsive action. These symptoms were not severe and were superficial.

Another group of men from the first showed chronic psychoneurotic reaction patterns, with episodes of psychosomatic symptoms, anxiety and mild depression. As a group their symptoms, personalities and basic problems were fairly similar. They responded well to ordinary psychotherapy and were of chief interest in that they reacted well to prolonged sea duty.

DISCUSSION

DR. T. L. DEHNE: Lieutenant Wigton mentioned the development of a chronic combat fatigue pattern. Is that too variable to describe, or could he present it in a few words? Do patients with combat fatigue look like civilian patients in chronic neurotic states? What is the prognosis for these patients? Do patients with combat fatigue go back to duty, and do they stand up well after their return?

Lieut. R. S. WIGTON (MC), U.S.N.R.: My colleagues and I used sedatives freely as needed, to assure adequate sleep and freedom from disturbing symptoms. Prolonged narcosis was not employed as the patients did not usually remain for extended periods. Narcosis treatment of patients with combat fatigue was limited by factors of time and numbers and was not often needed for control of disturbing symptoms. These usually subsided within a day or two. We felt that the patients were greatly aided by quiet surroundings, good food, hot showers and comfortable beds, as well as by interviews which gave them an opportunity to relate their experiences and to obtain relief from their tendency to self criticism and feelings of guilt through reassurance and explanation. The understanding and helpful attitude of the personnel of the ship as a whole was of great value. Chronic neurotic states were seen which were analogous to civilian neuroses. The combat fatigue syndrome developing in men without discernible predisposition differed clinically. In speaking of a more chronic combat fatigue reaction, I refer to the men who, after losing their acute dramatic symptoms, need further

treatment and rest for persisting startle reactions, impairment of self confidence and increased anxiety reactions to situations of stress.

We did not have the advantage of long observation of these patients and do not have first hand information concerning the further course of their illness. It is to be expected that their symptoms will gradually subside. More prolonged reactions are analogous to chronic anxiety states in civilian life.

Present Day Trends in Psychiatry. DR. KENNETH E. APPEL.

A number of cases from World War I, some from World War II and a civilian case were presented, to show what goes on in the therapeutic process of psychiatric disorders. In World War I, it was found that shell shock was not due to organic injury to the nervous system—the causes were factors of which the patient was unaware. Hypnosis was used in some cases. Rivers expressed the opinion that the patient should recognize and assimilate his terrifying experiences, and he was encouraged to do this in ordinary conversation. Consideration and understanding, rest and sympathy were found to be more important than intellectual formulation or explanation.

In World War II, a similar method is employed—a state of partial sleep is induced by the intravenous use of pentothal sodium. In this state the patient will talk of his experiences and express his fears or resentment, and with repeated use of this procedure he is relieved of his malignant tensions and in many cases can return to his company.

In the case from civilian life, a man, because of his early training, had become a perfectionist, and fear, hate and resentment had led to physical illness with bleeding ulcers, for which medical therapy was of no avail. Feelings of resentment and antagonism were allowed to well up in psychiatric interviews, and the ulcers healed and the fears disappeared. Many such patients recover after the recalling of forgotten events and the expression of intense emotion, without the development of insight. So one need not make therapeutic efforts too intellectual or consider insight as a criterion of recovery. Patients get a sense of security, protection, support and understanding on the part of the physician, and these factors are more important than specific drugs, reasoning and explanation.

DISCUSSION

DR. J. C. YASKIN: I am in agreement with Dr. Appel that psychotherapy for the majority of patients is a rational scientific procedure. Most patients, however, recover not because they obtain insight but, I believe, in spite of it, and most of the time without any intellectual insight. I am yet unable to form a clear idea of the mechanism by which the psychoneurotic patient improves with psychotherapy, but I believe the principles indicated by Dr. Appel apply to the majority of patients. I cannot escape the conclusion that in the everyday practice of psychotherapy suggestion and reassurance are important factors. The first value of the psychotherapeutic approach which Dr. Appel outlined rests on the fact that one can carry on for many hours without exhausting useful material, obtainable only through free association.

The treatment of patients with war neuroses should be somewhat modified. Such persons may be divided into two groups: patients destined to be psychoneurotic by prewar makeup and persons who become neurotic by reason of the hardships of war. The distinction is just as clear in this situation as it is in civilian life, in which two types of psychoneurotic patients are recognized; persons who have a psychoneurotic makeup of long standing, which emerges with some precipitating factor, and persons with true neuroses whose personalities are fairly well integrated. The psychoneurotic patient with a defective personality background reacts in large measure in war as he does in civilian life. With the patient suffering from a war neurosis the situation is different, since under stress of war conditions he acquires a so-called fatigue neurosis, which is practically equivalent to the problem of an acute anxiety neurosis in civilian life. Men with such a condition react satisfactorily with one treatment or another. In World War I many patients presented pure conversion symptoms. There were hundreds of men and officers with paralyzed legs who had no anxiety and were enjoying their situation. I saw hundreds get well on Nov. 11, 1918 who were not suffering from an acute anxiety state. With these men hypnosis, persuasion and good old-fashioned suggestion and shock were useful. Corpsmen were taught that when a new train arrived they were to tell the men they would get well in a few weeks, and it worked. Patients recovered in a matter of weeks, instead of months. Suggestion is an important mode of approach with some patients with these neuroses, but not with those who have severe anxiety.

Suggestion should still play a major role in the treatment of some neuroses in the war situation, even as it does in the physician's office, and I dare say patients are encountered for whom deep psychotherapy is not advantageous. Some patients with hysterical aphonias or paralyses react better to suggestion than to deep analysis. With some of these patients profound analysis is not conducive to therapeutic results.

DR. S. B. HADDEN: I appreciate Dr. Appel's presentation of this method of approach to the neurotic states, but I wish to express my disagreement with his comment that real cure can occur without development of insight. Dr. Appel and I may be speaking of the same thing from different points of view. I am sure that he does not refer to an intellectual type of insight—one with complete understanding of all mental mechanisms; I do not believe that that type of insight is necessary for cure, but I do feel that insight and understanding of the nature of behavior are necessary to recovery and that in Dr. Appel's case this occurred. By the free passive type of analysis, the patient is stirred to a voluble discussion of his early life, and his repressions and feelings of hostility may be verbalized; as this goes on, he gradually acquires a degree of emotional insight. As the result of emotional, rather than of intellectual, insight there is a more satisfactory appreciation and adjustment of his personality difficulties. Many times the patient does not know why he got well, but he was brought through an experience that gave him emotional, and not intellectual, insight. It is also important that many incidents that are most valuable in therapy the physician may not consider important at all. I am sure every one is interested to know why one does succeed in some cases. I had a rather dramatic experience of this kind with a minister of a very rigid sect. We had had several unsatisfactory interviews. One day he said, "Doctor, I should think that you, knowing that I am a minister and that I am opposed to smoking, would refrain from smoking in my presence." I said, "Why should I?" He was upset by my response but continued treatment. After he reached a certain point in the road to recovery, he said, "Doctor, I feel that I am getting better, but I thought I would

never improve under your care." I asked, "Why do you suppose you are getting better?" He answered, "You sort of burst my bubble. The day that you did not stand in awe of me, a minister, did something to me." My remark was certainly not a planned procedure, but it helped him to acquire insight into the fact that he was utilizing his ministry to cloak certain inadequacies.

I think that many times we psychiatrists lead patients through a passive analysis which does not give them understanding, or, as we call it, insight, but they have acquired a subconscious, an emotional, insight, which in my opinion is better than the intellectual insight. Many patients obtain real intellectualized insight which is of no use to them.

DR. F. H. LEAVITT: These cases are quite similar to those that I had while with the American Expeditionary Forces in France, in 1918. For such men as these, there were three neurologic field hospitals and, back of these, two neurologic base hospitals. It was found in the field hospitals, where the psychiatric patients were received early, and within a few miles of the front line area, that from 75 to 90 per cent of them could be returned to duty within about seven days. The majority of these patients were then said to have "shell shock," but at present the condition is termed "battle fatigue." There were also a number of patients with conversion hysteria, and success with them was variable. A regimen of regular feeding, sleep and psychotherapy did wonders to get these men back to duty; for the men who did not improve or get well within a reasonable time the prognosis was bad, and many of them were seen years later at the Veterans Administration Facility and at government hospitals.

Memorial to Dr. Charles W. Burr. DR. F. H. LEAVITT.

Dr. Charles W. Burr died on Feb. 19, 1944, at the age of 82 years. Dr. Burr was one of the founders of the Philadelphia Psychiatric Society and was president on three occasions. He was past president of the American Neurological Association and past president of the Pathological Society of Philadelphia. He served as professor of mental diseases at the University of Pennsylvania Medical School from 1901 to 1930 and was emeritus professor of mental diseases from 1931 to 1942.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, Feb. 25, 1944

Meningioma of the Lateral Ventricle: Report of a Case. DR. FRANCIS C. GRANT.

A white man aged 42 was admitted to the University Hospital on April 29, 1942, complaining of headache, ataxia, convulsions and fatigue. Because of interstitial keratitis he had been treated for syphilis for many years. Nine years prior to admission he noted that he staggered when he walked and began to have headache. Eight years before admission deafness developed. Five months prior to admission he noted tremor and weakness of the right hand, his headache became more severe and he staggered easily. Two weeks before admission he had a generalized convulsion, ushered in by a feeling of dizziness.

The positive neurologic findings were bilateral deafness, more pronounced on the left side; irregular, sluggish pupils; ataxic gait, and a questionable Babinski sign on the left side. The eyegrounds and visual fields were normal.

Roentgenographic studies of the head revealed nothing abnormal.

Air studies showed a complete block of the right ventricle, and the exploring needle demonstrated a resistant mass in this area.

Through a right temporoparietal bone flap and cortical incision, a purplish, discrete tumor, trilobular and forming a cast of the ventricles, was easily and completely removed. No attachment to the choroid plexus was noted. The tumor weighed 75 Gm.

Microscopic examination showed that the tumor was a fibroblastoma of the arachnoid.

Postoperative convalescence was smooth. The patient returned to work in six months and has had no further symptoms to date.

DISCUSSION

DR. N. W. WINKELMAN: I treated this man many years ago for neurosyphilis. At that time he had the interstitial keratitis and the deafness which he still manifests. I lost track of him about four or five years ago. I congratulate Dr. Grant on a brilliant diagnosis and surgical procedure.

The Scalenus Anticus Syndrome. DR. BERNARD D. JUDOVICH.

The scalenus anticus syndrome may be primary or secondary, the former usually being due to trauma and the latter associated with local lesions, such as tendonitis, bursitis or myositis.

A spastic scalene muscle may compress the subclavian artery, which lies in the acute angle formed by the muscle and the first rib. In rare instances an anomalous subclavian vein may be compressed. Tenderness of nerve pattern type may occasionally be encountered.

The symptoms, which consist of pain, numbness and a sensation of heaviness in the arm, tenderness, paresthesias and coldness of the hand, are correlated with the anatomic structures affected. In 1 case the pain of angina pectoris was simulated. In 2 cases compression of the subclavian vein simulated arthritis of the hand. In another case vasomotor instability simulated Raynaud's disease.

Diagnostic procedures include demonstration of tension and compression of the scalenus muscle; oscillometric dynamometric and cutaneous temperature readings, and the procaine test.

A new method of infiltration of the muscle with injection of procaine hydrochloride for diagnostic and therapeutic purposes is discussed. Factors which may cause a false interpretation of the test are a Horner syndrome and peripheral anesthesia following the injection of procaine. If either of these signs is present after injection, the test should be disregarded and the procedure repeated on another occasion.

Treatment includes repeated infiltrations of procaine, postural correction and surgical measures.

This paper was published in full in another journal (Judovich, B.; Bates, W., and Drayton, W., Jr.: *Am. J. Surg.* **63**:377 [March] 1944).

DISCUSSION

DR. H. E. YASKIN: If one observes a patient holding his hand over his head, with a sad expression on his face, one may anticipate cure by attack on the scalene muscle. Failure in some cases may be due to one of several factors, among which the functional element must play a major role. A neurotic patient may have localized pain. This is one source of therapeutic disappointment. Does Dr. Judovich have the number of patients he has actually treated?

DR. BERNARD D. JUDOVICH: The number of patients actually treated was over 100, and of these a number were relieved. Since my colleagues and I have changed our technic of injections we have had a high percentage of good results.

In the case presentered here there was no evidence of intraspinal lesion. Dr. Grant was not inclined to proceed with subarachnoid studies, and I feel that he was correct. Discoloration of the hand with involvement of three fingers in a patient who tends to carry his arm over the head points to an easy diagnosis, and the result of treatment is usually satisfactory. Our patients are treated with two or three injections of procaine. An occasional patient gets well without injections, and 1 patient in our group recovered with physical therapy, exercises and application of diathermy to the supraclavicular region. A diagnosis of compression of the scalene muscle does not always mean an operative procedure.

DR. GEORGE D. GAMMON: I should like to ask about the pain mechanisms involved in cases of this syndrome. I was glad to see that the author differentiated the relief obtained with infiltration of the muscle directly from relief obtained with production of the Horner syndrome and of anesthesia in the brachial plexus.

Dr. L. Kraeer Ferguson studied a similar group of patients at the university and reported to the section of neurology that the patient often did not get relief of pain unless he produced a Horner syndrome. Dr. Judovich is wise to separate the group who obtain relief from infiltration of the sympathetic fibers from patients who obtain relief from infiltration of the scalene muscle alone.

In another case, after injection into a section of scalenus muscle by Dr. Freeman, the patient was immediately relieved of her pain and did fairly well for two or three weeks. Suddenly there was a terrific attack of pain, lasting, I believe, from six to twelve hours, followed by weakness, with notable advance in atrophy in the muscles of the hand. It was as though there had been an interruption of the blood supply of the brachial plaxus. I wonder whether Dr. Judovich has had any similar experience.

Finally, I should like to ask what 2 cc. of procaine hydrochloride does to the muscle? Does it anesthetize the muscle itself? What evidence is there that it relaxes the muscle and relieves pressure? Would not the test of such an effect be a reverse procedure—injection of an irritating substance in the muscle, such as Lewis has done with a solution of sodium chloride, in order to see whether the pain was increased? It has been a question in my mind for some time just what the action of the procaine was, and I should like Dr. Judovich to comment on that, if he will. Is it necessary to infiltrate a muscle at the side of the entering nerve supply in order to obtain relaxation? Does it matter where the injection is made?

DR. BERNARD D. JUDOVICH: I do not know exactly what the procaine does except to paralyze the muscle temporarily, and this effect is palpable to the hand. The muscle is spastic before the injection and relaxed afterward. I believe it is tension against the vessel itself which causes pain. A good deal of pull would be needed to raise a patient's rib. We noticed, as I said, that we had operative failures in cases in which a Horner syndrome followed injection. We had a clue to this with a patient who showed a Horner syndrome after one injection and not after the other. She had relief with both infiltrations and was cured by operation.

We usually infiltrate the procaine at the lower end of the muscle, about 1 to 1½ inches (2.5 to 4 cm.) above the clavicle. The nerve supply comes from the third, fourth and fifth segments and sends branches into the muscle itself; I believe no nerves enter the lower end of the scalenus muscle.

DR. S. B. HADDEN: If Dr. Judovich had done nothing but call attention to the fact that in many cases of this syndrome the condition is secondary to some other painful lesion around the shoulders his presentation would still have been excellent, but he has done more. For the past seventeen years I have been associated with the police and fire department as consulting neurologist in the welfare department. Police and firemen are a breed unto themselves and have a large number of occupational diseases, this syndrome being one of them. I have reported before this society some of the curious disorders that policemen and firemen present. For example, a case of meralgia paresthetica is almost a daily occurrence, and the reason is apparent when I say that on several occasions I have weighed the pistol belt and pants of patrolmen and found them to weigh anywhere from 12 to 22 pounds (5.4 to 10 Kg.). In the course of the past seventeen years I have seen at least 200 cases of meralgia paresthetica. I have likewise seen a great number of cases of scalenus anticus syndrome. They are usually secondary to some other lesion around the shoulders, and the fact that certain policemen wear a shoulder holster, weighing from 7 to 10 pounds (3.2 to 4.5 Kg.), which swings on them at least eight hours a day is a factor. They come to me with myositis, or a painful shoulder if you will, and gradually secondary fixation, with contraction of the scalenus anticus muscle and this syndrome, is added. Many local conditions of the shoulder are associated with this condition, but almost inevitably there occur the elevation, fixation and secondary scalenus anticus syndrome. We have been giving injections in such cases, with surprisingly good results. We have discovered that there is not much use in injecting procaine into the scalenus anticus muscle alone and allowing other painful lesions around the shoulder joints to continue; these should be taken care of at the same time. Also, we have usually preceded and followed injection into the scalenus anticus muscle with the application of short wave diathermy and exercise. It is of the utmost importance, when the patient has been made free of this pain, to get him to exercise the painful shoulder, keeping it up for ten or fifteen minutes after the injection. I should say that our percentage of good results with that procedure has been about 75 or 80.

One must regard this syndrome as a secondary rather than as a primary disease, and it most often can be relieved without operation. Formerly a great many of our patrolmen were operated on, when it was fashionable to do so, but I believe that injection into the scalenus

anticus muscle for this and other painful lesions around the shoulder, combined with use of local heat and exercise, is giving relief in a much higher percentage of cases.

In how many cases did Dr. Judovich find the complication of occipital neuralgia? We have seen a great many such cases in the police department, for traffic policemen will stand on a windy corner for several hours, with their backs to the wind and coat collars turned up to protect their necks, and when seen will have occipital neuralgia, as well as all the classic symptoms of the scalenus anticus syndrome.

DR. BERNARD D. JUDOVICH: We find occipital neuralgia in about 15 per cent of our cases. We usually infiltrate the scalenus muscle; if the patient obtains relief from the occipital neuralgia nothing more is done. In other cases it may be necessary to infiltrate the occipital region.

DR. MICHAEL SCOTT: Perhaps the reason for the relief of the pain after injection of the scalenus anticus muscle is not the analgesia following the injection but, rather, the interruption by the anesthesia of the proprioceptive fibers in the muscle, resulting in loss of muscle tone, relaxation and therefore relief.

News and Comment

COURSE OF STUDY IN THE RORSCHACH TEST, MICHAEL REESE HOSPITAL

The course on the Rorschach test offered by Michael Reese Hospital, Chicago, is scheduled this year for the week of June 4 to 8 inclusive. The records to be demonstrated will be representative of the older adolescent and the younger adult, with especial emphasis on persons discharged from the military services. Dr. S. J. Beck, head of the psychology laboratory, will conduct the course. It meets twice daily, in two hour sessions. Interested persons may inquire of the secretary, Department of Neuropsychiatry, Michael Reese Hospital, 2908 Ellis Avenue, Chicago 16.

CANCELLATION OF MIDWEST CONFERENCE ON REHABILITATION

At the request of the War Committee on Conventions, Washington, D. C., the Institute of Medicine of Chicago has canceled its Midwest Conference on Rehabilitation, scheduled for Monday, February 12, at the Drake Hotel, Chicago.

Book Reviews

Crime and the Human Mind. By David Abrahamsen, M.D. Price, $3. Pp. 244. New York: Columbia University Press, 1944.

Inasmuch as there have been so few books written on the subject of crime in definite connection with psychiatry, any attempt to evaluate the conclusions derived therein must needs be guarded.

Statements in the preface would indicate that the author has had a rather enviable variety of experience, including work in criminology in Norway, association with the Illinois State Penitentiary and, lately, as a member of the staff of the Court of General Sessions, New York city.

The subject matter deals largely with a succinct and condensed review of the literature concerned with the criminologic, biologic, anthropologic and psychiatric (including the psychoanalytic) aspects of crime. The cultural and sociologic aspects also receive appraisal.

Having digested, or redigested, all of this material, one is still left with the main question unanswered, namely: What is the relationship between crime and psychiatry? As is admitted by the author, less than 10 per cent of criminal activity is accounted for by psychosis or mental deficiency. That criminals are deviates from the accepted average is axiomatic. Yet when one attempts to interpret the antisocial behavior of the criminal exclusively in terms of psychopathology, one almost invariably is obliged to fall back on conjecture. Aside from the psychotic and mentally defective personality, the author introduces a new classificatory label for the psychopath, namely, the neurotic character. As with the "compulsive psychoneurotics and psychasthenics," psychotherapy, or reeducation, is advised. Just how this recommendation is to be put into effect on any appreciable scale is not mentioned except through the author's allusion to the work being done in one or two dubious federal penal institutions. He does not go as far as Karpman and Zilboorg, who advocate prolonged psychotherapy in a mental institution for this group of offenders. He does strike a rather hopeful, though dubious, note, however, in averring that the psychopath, or his freshly substituted neurotic character, "provided no organic lesion is present, has a chance to mature and to adjust socially when [he reaches] forthy-five if properly provided with adequate institutional training."

In the final paragraphs, the author seems to grasp the crux of the situation when he states: "The behavior of the individual, be it a personal or a social maladjustment, is only a reflection of how disorganized society is." He fails to add, however, that these unhealthy cultural and educational influences have their origin in unhealthy concepts of parental and school training systems; otherwise, over 60 per cent of the offenders would not begin their criminal preoccupations during their period of exposure to these systems.

As to remedial measures, certainly individual psychotherapy, as administered in mental hygiene and court clinics and in prisons, has effected little, if any, diminution in the incidence of crime; nor have the indirect therapeutic methods, such as are utilized in the probation, parole and reformatory systems, brought about any appreciable abatement in criminal offenses.

It is to be hoped that the author may produce a supplementary volume analyzing these faulty training methods and therein make appropriate recommendation as to constructive alterations.

The book should be of assistance to the student of criminal psychiatry.

La oliva bulbar; estructura, función y patología. By J. O. Trelles. Pp. xi plus 105, with 46 illustrations. Lima, Peru: Editorial Lumen, 1944.

In this handsomely printed monograph, Trelles has summarized what is known about the inferior olive, much of it based on his own researches in Paris. It seems that much more is known of the anatomy and pathology of this prominent structure than of its function. However, new light has been shed on its function during the past decade, since the concurrence of olivary hypertrophy and palatal myoclonus has been established. This is shown in the 28 cases collected by the author. Concurrent lesions, however, have complicated the problem. In most cases of palatal myoclonus there have been lesions of the central tegmental fasciculus on the same side; but in a minority of cases the contralateral dentate nucleus has suffered, and in 1 case neither structure was affected. Moreover, not all lesions of the fasciculus or of the dentate nucleus are sufficiently severe to provoke the hypertrophy. When it occurs, the hypertrophic change may commence within a week of the exciting lesion and may last for years. The olivary hypertrophy not only is gross but includes the ganglion cells, which undergo extraordinary reduplication of processes and peculiar distortions, as shown by drawings and by photomicrographs. The author designates these changes as gigantocytosis with paraphytosis and compares the mechanism with that observed with certain lesions of peripheral neurons. He leans away from the transsynaptic degeneration theory, since he has shown a well defined connection between the dentate nucleus and the opposite olivary body by way of the superior cerebellar peduncle.

Preliminary chapters deal with the anatomy and connections of the olivary body and the developmental aspects through the vertebrate series and in the individual organism. Sclerosis of the olivary nucleus may occur in particularly prominent fashion in dementia paralytica, and may thus underlie the dysarthria of this disease. Senile changes in the olives are common, but senile plaques are not encountered. On the other hand, in myoclonus epilepsy the cells are always affected, sometimes in isolated fashion. Isolated degenerations of the olivary bodies occur rarely and are accompanied by rigidity and tremor. More frequently, the olives are involved together with the cerebellum and other structures in the well known system diseases. A good bibliography and author index complete the work. While it is apparent from this monograph that lesions of the olive are associated with disturbances in muscular function in the nature of myoclonias, tremor and rigidity, the function of the olives in assuring smooth and coordinated action of the various muscles still remains much of a mystery.

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VISUAL DISTURBANCES PRODUCED BY BILATERAL LESIONS OF THE OCCIPITAL LOBES WITH CENTRAL SCOTOMAS

LIEUTENANT COMMANDER M. B. BENDER, MC(S), U.S.N.R.

AND

COMMANDER L. T. FURLOW, MC(S), U.S.N.R.

Experience in the last war has shown that injuries to both occipital lobes result in total blindness. The blindness, however, is rarely permanent.[1] As a rule, there is progressive restitution of vision although recovery is seldom complete. In many cases careful perimetric examination may reveal residual scotomas in the homonymous fields of vision. The degree of partial blindness depends on the extent of the damage to the calcarine cortex. In addition to field defects, certain physiologic and psychologic mechanisms of vision may become apparent in these cases through special examinations. Interesting descriptions of qualitative and quantitative changes in restitution of visual function may also be volunteered by the patient. Recently, we had the opportunity to study several persons with battle wounds of both occipital lobes. One of the patients presented a remarkable clinical picture throughout the period of recovery, and his case is herewith described in detail.[2]

REPORT OF A CASE

History.—A Marine, private first class, aged 23, was struck in the occiput by enemy gunfire. As soon as he was hit, he fell and apparently lost consciousness. He was given emergency treatment, and when he recovered, within several hours, he was totally blind, unable even to see light. Two days later he appreciated light, but everything appeared to him to be a "milky haze or dense fog." He could not recognize any movement until nine days after the injury.

Examination.—Physical examination at an overseas base hospital revealed two almost healed, clean bullet wounds, each located exactly 1 inch (2.54 cm.) superior to and 2 inches (5 cm.) lateral to the right and the left of the inion of the occiput. The hole on the right side was larger than the one on the left, and, according to the records, the direction of enemy firing was from the patient's right side. The right pupil measured 5 mm. and the left pupil 3 mm. Both responded to light, but the left one reacted better than the right. There was no ptosis or palsy of the ocular muscles. A transient nystagmus was noted, especially on lateral gaze to the right. Both optic fundi showed papilledema. Grossly, no definite visual defects could be plotted. Subjectively, the patient felt that he was perceiving with his central fields of vision. The rest of the neurologic examination gave essentially normal results. A roentgenogram of the skull disclosed two irregular defects in the left and right occipital bones respectively, with intercommunicating fracture lines between the two. In addition, bony fragments were noted to extend intracranially for 2 cm. from the occiput (fig. 1 *A*). Ventriculographic examination, performed because of papilledema, showed slight upward elevation of the right posterior horn (fig. 1 *B*). There was no evidence of subdural or subarachnoid hemorrhage, and on the surface the cortex appeared normal. The patient was treated conservatively and continued to improve.

Progress.—Thirty-five days after the injury the patient was able to appreciate the presence and contrast of objects in his surroundings. He made the interesting observation that his vision seemed to be equally good in the central and in the peripheral part of the field of vision. All objects, however, appeared to him to be obscured by a "dense fog." Special psychologic tests showed no intellectual impairment. Comprehension and reaction times were normal. Physical and neurologic examination showed no deviation from previous records except that the papilledema had receded.

Forty-three days after the injury a craniotomy was performed, and fragments of bone were removed from the left side (fig. 2). The cortex of both occipital poles was observed to be damaged, and the adjacent subcortex on the right side showed a large degenerative cyst. One week later the patient complained of numbness, tingling and inability to recognize objects in the finger tips of either hand. Examination disclosed bilateral impairment of stereognosis, position sense and two point discrimination. These defects were mild and transient. His vision continued to improve.

Two months after the injury rough perimetric examination disclosed large, absolute central scotomas in both eyes, each surrounded by relative scotomatous defects. The latter seemed to be less intense toward the periphery of the field of vision. Unconsciously,

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1. Klüver, H.: Visual Disturbances After Cerebral Lesions, Psychol. Bull. **24**:316-358, 1927. Wilbrand, H., and Saenger, A.: Die Verletzungen der Sehbahn des Gehirns mit besonderer Berücksichtigung der Kriegsverletzungen, Wiesbaden, J. F. Bergmann, 1918.

2. The other patients in this series revealed similar symptoms, but to a lesser degree.

the patient had a great tendency to fix with his peripheral field of vision. He was unaware of the large scotomas in his central fields of vision, and he could not be convinced that he was actually seeing with his peripheral retina. To him objects appeared to be in the middle of his field of vision. One week after this examination the fields were plotted on a tangent screen at a distance of 1 meter, ocular fixation being maintained with his peripheral field of vision. These fields showed scotomas extending 20 degrees from the central point for motion of a 10 mm. test object. There was no color perception. Peripherally, he could detect motion, direction of movement and objects described by motion, such as a drawn circle, a triangle, the number 4 and the letter A He claimed that whatever vision he had seemed to be clearer with low illumination.

Ten weeks after the injury he began to notice large print He was still under the impression that he saw with his central field of vision The image was indis-

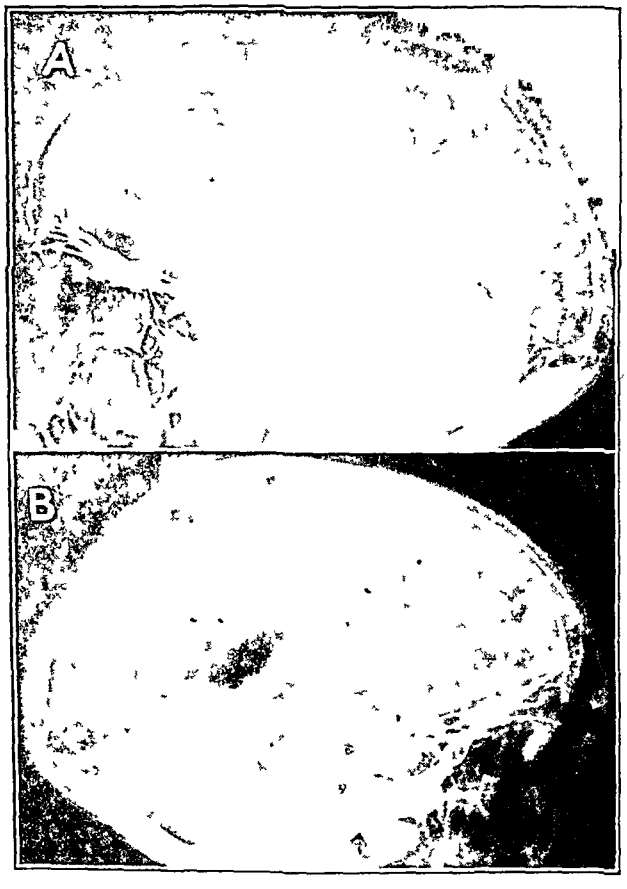

Fig 1—*A*, roentgenogram of the left side of the skull, revealing defects and scattered fragments of bone extending intracranially from the occiput. *B*, ventriculogram of the right side, showing elevation of the posterior horn of the right lateral ventricle.

tinct, and all he could actually distinguish was contrast between black and white. Color perception had not yet returned Opticomotor nystagmus could be elicited when he fixed with his peripheral field of vision.

Eleven weeks after the injury the patient volunteered that he saw much better at night or in the dark, when he could recognize objects, and even some color. On cloudy days or at dusk he could count fingers and thought he could identify red and yellow in the peripheral portion of the left field of vision Dark adaptation time measured on the Feldman adaptometer was nine minutes. Subsequent examinations by other methods also showed prolongation of the dark adaptation time.

Three months after the injury the visual fields were plotted on a tangent screen at a distance of 35 cm. under illumination of 3.5 foot candles. The size of the test object used was 10 mm. The plotted fields revealed large bilateral central scotomas extending 15 degrees from the central point. The absolute scotoma was surrounded by concentric zones of relative loss of vision, the defects being less conspicuous toward the periphery of the field of vision.

Six months after the injury the extent of the central scotoma remained unchanged. In the left upper quadrants of the fields of vision the patient was able to recognize a yellow pencil with a small red top. This image, he claimed, fluctuated in brightness and clearness. Seven months after the injury, in the right upper quadrants he identified the color of small test objects (fig. 3). In other quadrants he recognized form and shape, such as geometric figures or letters of the alphabet.

From this time he was able to walk about without assistance. He was not, however, certain or confident of walking unaided in the street. Further recovery was slow. The visual fields were practically unchanged. Five months after the injury after-imagery could not be induced irrespective of the quantity or quality of the light stimulus applied.[3]

Fig. 2.—Roentgenogram of the left side of the skull after removal of fragments of bone.

COMMENT

In order not to lose the significance of the signs and symptoms noted during the convalescent period, each will be described and discussed under its own heading.

Perception of Light.—The first visual function, which returned two days after the patient was injured, was that of light perception. He stated: "What I saw was a milky fog." Everything before him seemed to be a glare. A bright

3 In the cases of patients with less extensive defects of the central visual field, after-imagery could be elicited, but the responses varied. In a patient with three fourths of his binocular field of vision defective, the shining of a round light into either eye produced an angular or square, gray image, which showed no fluctuation in color except for a transient maroon, a blue tint or a darkening of the tone of gray.

object or sunlight was unpleasant to him. He constantly sought shady areas and avoided sunlight because he felt more comfortable in the dark. For this reason, he independently purchased dark lenses and wore them religiously during the day. He claimed he felt better on cloudy days and at night. Three months after the injury he noted that he perceived movement or outlines of objects best in the dark or at night. He stated: "I can see better in total darkness. At times I could see the outline of a flying airplane at night. When I come out of a dark room into a bright room, my eyes hurt, and it makes me blink." He also found that he recognized an object with a dark background better than when it was silhouetted against a light or a bright field. Under bright illumination he identified the presence of an object better when it was Brightness also interfered with his perception of color and form, and even of motion. Interesting psychologic reactions were the unpleasant emotional experiences he had while exposed to illumination and his relative sense of security and calmness when in the dark.

Perception of Movement.—Almost as soon as the patient was able to distinguish between light and dark he recognized movement of large objects, such as the waving of a hand or an arm in his peripheral fields of vision. Five weeks after the injury the patient noted that he could "guess" at objects in his surroundings, such as pieces of furniture, but only while he was in motion. When he was standing still he did not see much. This is an example of appreciation of relative movement. Everything before him appeared foggy, and he did not even attempt to

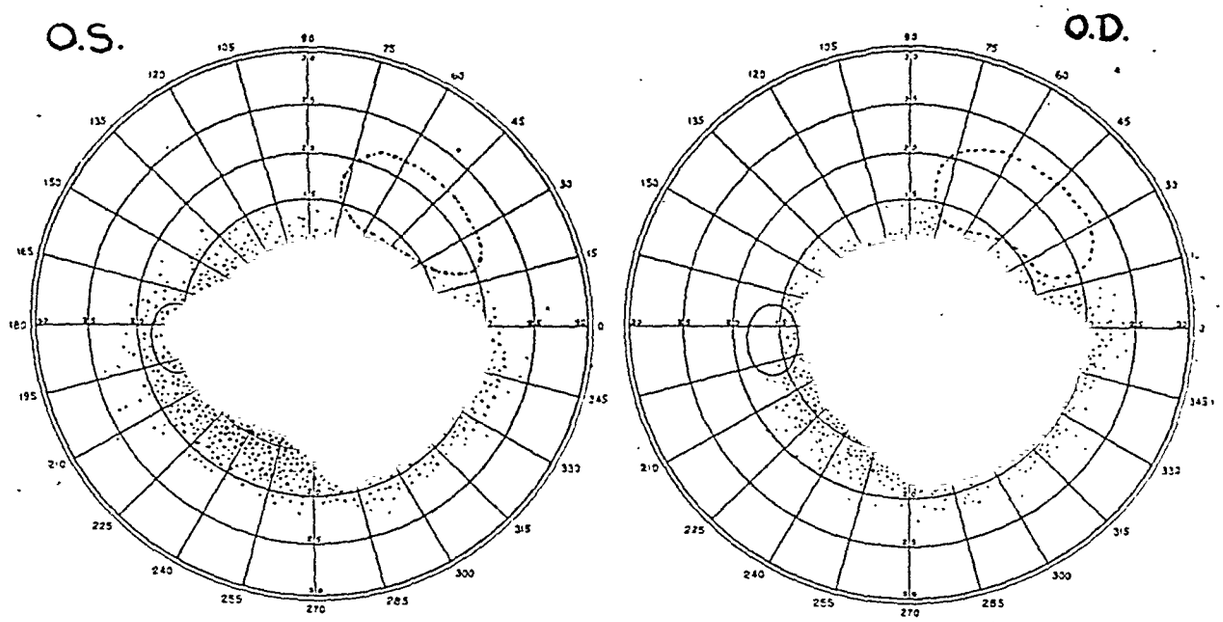

Fig. 3.—Visual fields plotted on a tangent screen six months after injury to both occipital lobes. Size of test object, 10 mm.; distance, 35 cm; illumination, 3.5 foot candles. The solid black area represents absolute scotoma, and the stippled area, relative blindness, which is most pronounced centrally and less evident toward the periphery. The line of dots represents an area in which color vision was preserved. The patient was able to recognize the shape of large objects in the left inferior quadrants and the color of large test objects under low illumination in parts of the upper and lower quadrants of the left fields of vision.

in motion. Obviously, on sunny days his vision was poor.[4] Later in the stage of his recovery, he complained that the glossiness, luminosity or brightness of an object interfered with his visual recognition, or even with his "desire" to perceive the object.

Since central vision was destroyed the patient was day blind. What vision he possessed seemed to function best with low illumination; and since this condition is characteristic of the peripheral part of the retina, it confirms the results of examination of the visual fields, namely, loss of central vision and retention of peripheral vision due to damage to the occipital cortex.

4. This was also true of other patients with battle injuries of both occipital lobes.

look at stationary objects. He was under the constant impression that he perceived movement with his central fields of vision. Repeated examination, however, showed that he was totally blind in the central fields of vision and that he appreciated movement keenly in the peripheral fields. In fact, here he was able to perceive form and shape of objects delineated by movements. He recognized only geometric figures, letters or numbers when they were drawn in the peripheral visual fields. Often, he reflexly tilted his head and eyes so as to regard the moving object in question with his paracentral field of vision.

Biologically, appreciation of movement is one of the most primitive forms of visual functions

and one of the most essential features in the vision of lower animals. It is a function par excellence of the peripheral portion of the retina. Our patient manifested all the physiologic functions of this part of the retina—in his case, the peripheral "cortical retina." He had no central vision. It is apparent from this case that in man, too, appreciation of movement is well developed in the peripheral fields of vision, but his visual perception in general depends largely on recognition of form, a function of central vision.

Perception of Form.—The power of identifying the form or shape of objects is based on visual acuity, experience and interpretation. Since visual acuity is highest in the central field of vision, it is obvious that appreciation of still objects is achieved mostly with the macula and least with the peripheral field of vision. Because our patient had no central vision, he did not have much perception of stationary objects. However, he recognized the shape of familiar objects described in motion in the peripheral fields of vision. Thus, on the basis of experience and memory, he was able to interpret the form and shape of an object outlined by movement. He could not discern unfamiliar objects in this manner. In other words, the patient had perception of form with his peripheral vision, but only through the medium of appreciation of motion.

As the central scotoma contracted, and the visual acuity improved, he learned to identify the size and shape of immobile articles. Thus, six months after the injury he guessed correctly the shape and color of a pencil exposed in his paracentral field of vision. After seven months he perceived, without too much difficulty, the shape of a 2 inch (5 cm.) square or circle and the letter H when presented in the left homonymous fields of vision, about 20 degrees from the fixation point. He failed when presented with unfamiliar drawings, such as Roman numerals or a mirror-imaged *E*.

During the period of recovery he showed an interesting psychologic mechanism. He had a great tendency to fill in defects in his visual perception. Even when he had little vision and images were not clear, it seemed to him that he saw the whole object. Thus, when he was presented with a familiar article, he felt certain that he saw it completely and proceeded to describe its gross shape, and even color. The description was frequently correct; but when he was confronted with an unfamiliar object, he failed in his endeavors. In fact, he did not even attempt to look at the exposed object. Evidently, the apparent appreciation of form was based largely on experience and meaning, and only partly on the acuity which was present in small islands in his peripheral field of vision. Psychologically, he respected the fact that he could not see, and thus he avoided situations which would elicit his failures in vision. He tackled only images which appeared familiar. What the patient's symptoms demonstrated here was the principle of gestaltism, or that of appreciation of the form of an object as a whole by psychologic filling in of the defects of the perceived retinal image.[5]

Perception of Color.—The patient had no color perception until eleven weeks after the injury, when he began to guess at colors of very large objects. Thus, he "thought" he saw a yellow pencil, declaring, "I believe I can see some color. I think I can see the yellow in that pencil." After that incident, he began to search for color by turning his head and eyes so as to fix with his peripheral fields of vision, and he noticed that he discerned color better under poor illumination. Thus, one night when a plane crashed, the patient claimed he saw the red glow of the fire. At first his appreciation of color was poor, and the only one which he seemed to name correctly was red. Otherwise, everything appeared to have a gray tone. However, he improved, and five months after the injury he recognized red, green and blue neon signs. Plotted visual fields at this time disclosed an island of color vision in the right homonymous superior quadrants. He identified correctly red, blue and green 1 degree test objects at a distance of 27 cm. and under 3.5 foot candles of illumination 15 degrees from the macula.

Appreciation of colors is not a uniform function of the retina. When the eye is light adapted, the extreme periphery of the retina is monochromatic, or color blind. This, however, is only relative. If the stimulus is feeble, color sensation is absent in all parts of the retina. If the intensity of the light is increased, the field gradually extends until eventually most colors become apparent at the periphery. In a similar manner, variation of the area or size of the tested color objects influences the extent of the field for color vision. In general, color vision is less sensitive in the peripheral than in the central part of the fields in the light-adapted eye.[6] In our patient, the chromatic response in bright illumination was nil, an observation seemingly contradicting the foregoing statements. However, it must be remembered that our patient was relatively day blind and

5. Goldstein, K.: After-Effects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942.

6. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938.

that his remaining vision depended on peripheral retinal function. Also, bright illumination or a glare produced a psychologic resistance to visual perception, and thus it could not be determined with certainty whether the patient could or could not appreciate color in the light-adapted eye.

Under conditions of dark adaptation color sensitivity is also greatest in the macular region, but it falls off much more rapidly and is much more restricted toward the periphery. Of all colors, sensitivity to red, however, extends to the extreme periphery.[6] This should explain why our patient saw the red glow of a burning plane at night twelve weeks after the injury. In summary, it appears that the patient's responses to color stimuli were the responses expected of a person with visual function limited to the peripheral field.

Subjective Visual Phenomena.—As previously noted, the patient disliked to look at bright objects or illuminated areas. He claimed it was disagreeable and that it interfered with the little vision he possessed. Three months after the injury, he stated: "When I look straight ahead, I see heat waves rising in front of me. The waves seem to be directly before me. I cannot tell whether or not I see better with the side of my eyes. Sometimes it seems as if the sun were shining on ice, and little spots of moisture were rising." He first noticed the appearance of these waves soon after "foggy vision" began to improve. Subsequent observations by the patient disclosed that he saw these "moving heat waves," or "radiations," every time he gazed at a bright background.[7] The more intense and brighter the sun, the more vivid were the emanating waves before him. The rate of radiation of the "heat waves" seemed to increase with the luminosity of the background. With this increase in radiation there was a decrease in visual perception of objects in his surroundings. The patient stated: "The more sunlight there is, the thicker and denser the waves and the greater the haze before me. Increased light makes the radiations, which seem to go upward in a spiral, move faster. These waves are made up of circles all mixed up and moving in all directions, but they seem to be going chiefly upward."

What this patient described were phenomena of entoptic vision. It is well known that if a brightly illuminated surface, such as the sky or a fluorescent screen, is regarded by the normal subject, a great number of small, bright dancing spots appear on a relatively dark background, shooting upward, darting rapidly along a circuitous path and disappearing as abruptly as they come. According to one theory these images are due to visibility of red blood corpuscles, or the spaces between them, moving through the capillaries.

About five months after the injury, the patient remarked that when he looked at an object directly before him, it tended to wax and wane; he declared: "The object fades quickly and becomes somewhat clearer in a short time. When it fades, it becomes grayer. When it gets clear, it appears darker gray and less foggy." When the patient fixed on an object, such as a large pencil, in ordinary room light, he described periodic variations in the perceptible visual acuity. This fluctuation in visual perception is a normal phenomenon and may be easily demonstrated under certain conditions.[8] It is more evident with threshold stimuli.

Orientation of Field of Vision.—Psychologically, the patient showed an interesting phenomenon, that of persistent displacement of the perceived image from the seeing peripheral to the nonseeing central field of vision. Throughout his period of convalescence the patient felt that he perceived objects in space, although not clearly, just as he always had prior to the injury. He insisted he saw objects directly before him with the central parts of his fields of vision. It was difficult to convince him that his central fields were totally blind. He was unable to detect the blind areas when he viewed articles or people before him, and it seemed that he made no effort to search for the scotomas. Everything before him seemed to be of uniform visual intensity. In gross tests, a large central absolute scotoma could be elicited in each eye. This was demonstrated to the patient on repeated occasions throughout the period of convalescence, but only with great reluctance did he accept the fact that there was no vision in this zone. In spite of this admission, six months after the injury, he still declared, "I cannot see any black spot or blind area before me. I still do not believe I am blind in the center, though you proved it to me. People tell me I move my eyes around when I try to look at things; so I must be using the side of my eyes, but even then it is hard to believe."

This is a type of disturbance in space perception in which the localization of an object is relative; the perception of a point in the subjective visual space is relative to the fixation point. A patient with scotoma has his visual

7. Other men with bilateral lesions of the occipital lobe had similar subjective visual phenomena. One of them had such symptoms even with the eyes closed.

8. Guilford, J. P.: Fluctuations of Attention with Weak Visual Stimuli, Am. J. Psychol. **38**:534-583, 1926.

fields psychologically organized in the same manner as has a normal person. As Klüver put it: "There is a 'right' and 'left' side, and 'above' and 'below' and a special center which is 'straight forward' or 'just before me'" in the remaining field of vision. The special center is in the perceptive zone and determines the subjective median point, whereas the objective median point may lie in the blind field. However, in our patient the subjective median point was projected psychologically into the blind field because there was no zone of remaining vision which had the power to perceive form or to hold his attention. He was unable to establish a pseudofovea, that is, a fovea in the functional sense, until he could appreciate size and shape of objects with a part of the residual field of vision. When such restitution became manifest, seven months after the injury, he formed a new center of distinctness, or a new functional fovea, and he no longer projected his subjective median point into the blind macular area. His psychologic field of vision became reorganized about the new functional macula. Interestingly, when a new functional fovea was formed, he could be convinced that he was using his peripheral vision, and he finally admitted that people "must have been right" when they told him he was moving his "eyes around in looking at things." In other words, not until his psychologic field of vision was reorganized did he relinquish his old pattern of vision.

SUMMARY

1. A patient with bilateral lesions of the occipital lobe showed a series of visual disturbances due to loss of central vision in each eye. After he had been completely amaurotic, vision returned in the peripheral fields, and restitution continued to take place medially, terminating in bilateral large central scotomas. During his period of recovery he had good perception of motion, defective color vision, little appreciation of form and ability to see best in the dark or in low illumination, all visual functions characteristic of the peripheral portions of the retina (in this case the peripheral "cortical retina").

2. The patient also manifested (*a*) the normal mechanism of psychologic filling in of visual field defects, thus perceiving objects as a whole; (*b*) retention of his psychologic field of vision about a subjective central point in a blind area, which made it difficult for him to realize that his central vision was lost; (*c*) reorganization of his psychologic field of vision when a new functional fovea was formed; (*d*) entoptic phenomena, with visualization of emanating "waves" and (*e*) fluctuation of perception in the remaining field of vision.

3. Opticomotor nystagmus was induced by having a striped drum revolve in his peripheral, but not in his central, fields of vision. Five months after the injury after-imagery could not be elicited with a light stimulus placed in any part of the field of vision.

VASOTHROMBOSIS OF THE CENTRAL NERVOUS SYSTEM

A CHARACTERISTIC VASCULAR SYNDROME CAUSED BY A PROLONGED STATE OF VASOPARALYSIS

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Putnam and his co-workers [1] were the first to call attention to the importance of local circulatory disturbances caused by venous obstruction, and they demonstrated clearly its significance in cases of disseminated sclerosis. Putnam has approached the subject from many different avenues and has established important data extending far beyond the problem of pathogenesis of multiple sclerosis. It is surprising how few histopathologic studies concerning the alterations of the venous circulation in the brain are available. Several aspects of the morphologic characteristics of venous thrombosis and its pathogenesis remain obscure. One needs particularly to know more of the early stage of the pathologic process.

It is the purpose of this presentation to report observations in a series of cases in which thrombosis was confined to the smaller veins and capillaries and to discuss the pathogenesis of the lesions. Special attention will be paid to the earliest manifestation of the pathologic process and to the relation to "vasoparalysis of the central nervous system," a recently described vascular syndrome.[2]

REPORT OF TWO ILLUSTRATIVE CASES

CASE 1.—A Negro woman aged 23 was first admitted to the Cincinnati General Hospital on Sept. 6, 1938, with the following history: She was in excellent health until three days prior to admission when coincident with the onset of menstruation, she noticed tingling and numbness in both lower extremities. Two days later she complained of weakness of the left half of her body and was not able to raise her left leg off the ground. She noticed that objects slipped from her left hand and that her grip was weak. On walking she tended to fall forward and would occasionally stumble in going up the stairs. On the morning of the day of her admission to the hospital she fell out of bed twice and noted altered sensation in the left half of her body and numbness and tingling in her left upper extremity.

The only abnormal findings on examination at the time of admission were those associated with left hemiparesis. There was moderate to pronounced weakness of all movements of the left extremities and of the lower portion of the left side of the face. The resistance of the left extremities to passive movement was increased slightly. The patient reported that pinprick was better perceived on the right side of the face and trunk and the right extremities than on the left side, and that pinprick on the left side felt definitely abnormal and "stingy." The left corneal reflex was reduced slightly. The deep reflexes were hyperactive, the exaggeration being slightly greater on the right side than on the left. The left abdominal reflexes were absent. The left plantar responses were of extensor type.

The pulse rate ranged around 90 per minute. The blood pressure was 138 systolic and 76 diastolic. The cerebrospinal fluid was completely normal; the Kahn reaction of the blood was negative. Examinations of the urine, stool and blood gave normal results. An electrocardiogram was interpreted as indicative of myocardial damage.

The patient remained in the hospital until September 10. Strength in the left extremities increased slightly during the five days in the hospital, but she never was able to walk without assistance, and she dragged her left foot along the floor.

The family noted that she was never able to return to work after her discharge from the hospital, on September 10, since the entire left side remained paretic. She could move her fingers and her left leg, but she could bear no weight on the latter; when she stood she had to hold on to something. In late October her left great toe would go into spasms of dorsiflexion and, according to the relatives, caused the patient considerable pain; she would scream during these episodes.

For a few days before her readmission to the General Hospital, in early November, she was delirious. The weakness, which had been limited to the left extremities and the left side of the face, spread to involve the right limbs a week or two before the readmission. She became unable to feed herself; and, though she could move the fingers slightly, she could not use her hands and was unable to lift either arm off the bed. About November 1 she became incontinent of stool and urine. She was readmitted to the hospital on November 5. At this time she was relatively unresponsive,

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786, 1933; Evidence of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

2. Scheinker, I. M.: Vasoparalysis of the Central Nervous System, a Characteristic Vascular Syndrome: Significance in the Pathology of the Central Nervous System, Arch. Neurol. & Psychiat. **52**:43 (July) 1944.

listless and dull. She seemed to recognize that questions were being asked and tried to answer, but she usually ended with stereotyped exclamations. At times she answered questions, but to most she gave fragmentary responses, and these were stereotyped; on some occasions she was considered to be aphasic. Speech was slurred Sometimes she broke into laughter on being questioned. There was increased tone in all the extremities, particularly on the left side. She was occasionally able to move one extremity or the other, and it was determined that all the extremities were considerably weakened. There was weakness of the right lower part of the face. She could not sit up without support. It was practically impossible to test sensation. The deep reflexes were hyperactive. The abdominal reflexes were absent. There was bilateral forced grasping. The Hoffmann responses were obtained bilaterally, and the plantar responses were extensor, more obviously so on the left side.

On November 8 the patient used the correct words in singing songs, and she was able to move her upper extremities fairly well. For the most part her extremities rested in flexion and were spastic. Attempts to straighten a flexed extremity resulted in moans. Drooling of saliva was occasionally noted. Stertorous respiration, with a rate of 44 and an accompanying pulse with a rate of 140 per minute, made its appearance on November 11. Thereafter the temperature and respiratory rate, which had been relatively normal, rose steadily, and the patient refused nourishment. The neck and trunk became rigid. She was noisy at times and stuporous at others. After November 11 fluids had to be administered parenterally. She continued in an extremely precarious condition until November 16, when frequent convulsions were noted. Signs of lobular pneumonia made their appearance four or five days before death. She became comatose on November 13 and cyanotic on November 15, at which time she was placed in an oxygen tent. She died on November 17, seventy-four days after the initial symptoms of her illness.

Fig. 1 (case 1).—Tremendously distended small vein, with signs of stasis. Note the beginning degeneration of the vessel wall and the early stage of edema and rarefaction of the surrounding tissue. Hematoxylin and eosin stain; × 225.

Autopsy.—The pathologic changes, exclusive of the lesions in the nervous system, were lobular pneumonia and fatty infiltration of the liver.

Examination of the nervous system was limited to the brain. The subarachnoid membrane showed slight brownish discoloration and moderate thickening. The meninges at the base were not remarkable The configuration of the circle of Willis was normal, and the vessels did not disclose any gross alterations.

Coronal sections throughout the brain displayed obvious displacement of the ventricular system from the left to the right and widening of the white matter. The left cerebral hemisphere measured 7.2 cm. from the midpoint of the corpus callosum to its surface; the corresponding measurement for the right hemisphere was 4.9 cm. The basal ganglia on the left side appeared almost twice the size of those on the right. There was evidence of an intense and generalized congestion associated with numerous small petechial hemorrhages, throughout both the white and the gray substance, particularly noticeable in the swollen left hemisphere.

Microscopic Examination.—Sections were taken for survey from several areas of the gray and the white substance of both hemispheres and from the midbrain, pons and medulla. All sections were stained with hematoxylin and the Van Gieson stain, phosphotungstic acid hematoxylin, the Loyez stain for myelin sheaths and the Bodian 1 per cent strong protein silver method.

Histologic examination disclosed (1) vascular lesions and (2) alterations in the nerve tissue proper.

1. Vascular lesions. These consisted in maximal dilatation and congestion of the capillaries and small veins; they were engorged with blood and showed all the signs characteristic of vasoparalysis (fig. 1). In addition, many of the smaller blood vessels revealed degenerative changes or complete necrosis of the vessel wall, with increased permeability for serous fluid and red blood cells.

The most striking manifestation of the circulatory disturbances was the presence of early stages of thrombus formation, as illustrated in figures 2 and 3. The lumens of numerous small veins were completely occluded with blood clots, composed of curved strands of fibrin mixed with large masses of platelets and white blood cells. In some of the veins the clot seemed to be slightly attached to the intima. The vessel wall appeared well preserved except for slight loss of stainability of its cellular elements. Some of the veins contained only a relatively small number of fibrin threads, numerous platelets and a large mass of granular debris formed by broken-down white blood cells.

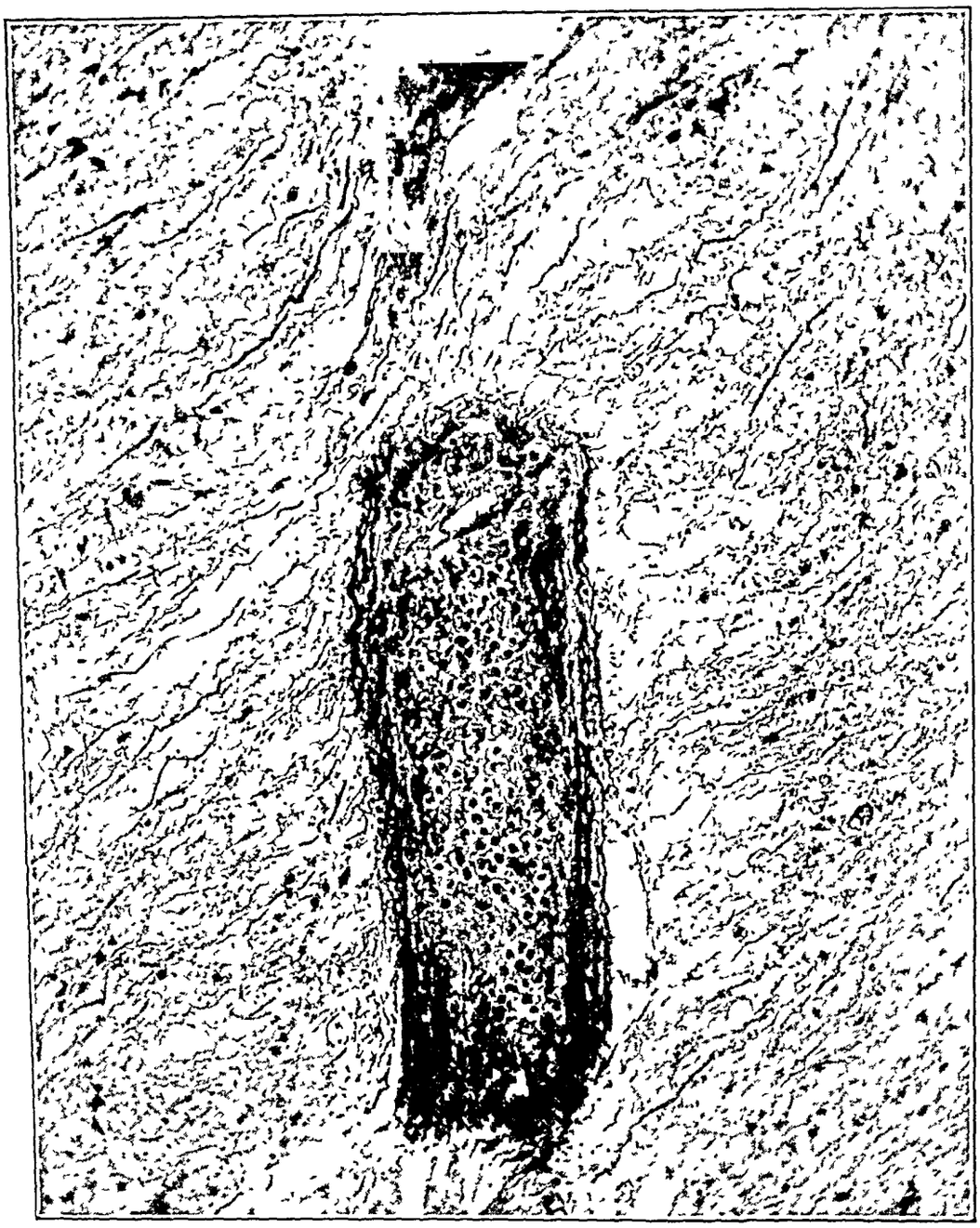

Fig. 2 (case 1).—Small vein completely occluded by a blood clot composed of large masses of platelets mixed with white blood cells and curved strands of fibrin. Note the tissue disintegration of the nerve parenchyma. Hematoxylin-eosin stain; × 225.

Late stages of thrombosis, such as organization with connective tissue, could not be seen. These various vascular lesions were noted throughout scattered areas of the brain and were more noticeable in the pial veins and the small vessels of the cortical ribbon, though present also in the subcortical white matter of the left hemisphere.

2. Changes in the nerve tissue proper, secondary, I believe, to the circulatory disturbances, consisted mainly of widely disseminated areas of softening involving the large veins. The cortex of the softened area showed several layers: First, there was a layer of dense glial reaction occupying the molecular zone, which was densely filled with glia cells, mostly astrocytes with large protoplasmic bodies and many processes. Some large veins perforated this layer. The entire deeper part of the cortical ribbon was completely destroyed and replaced by a large number of fatty granule cells and newly formed capillaries. The larger perforating vessels disclosed signs of stasis and were occasionally

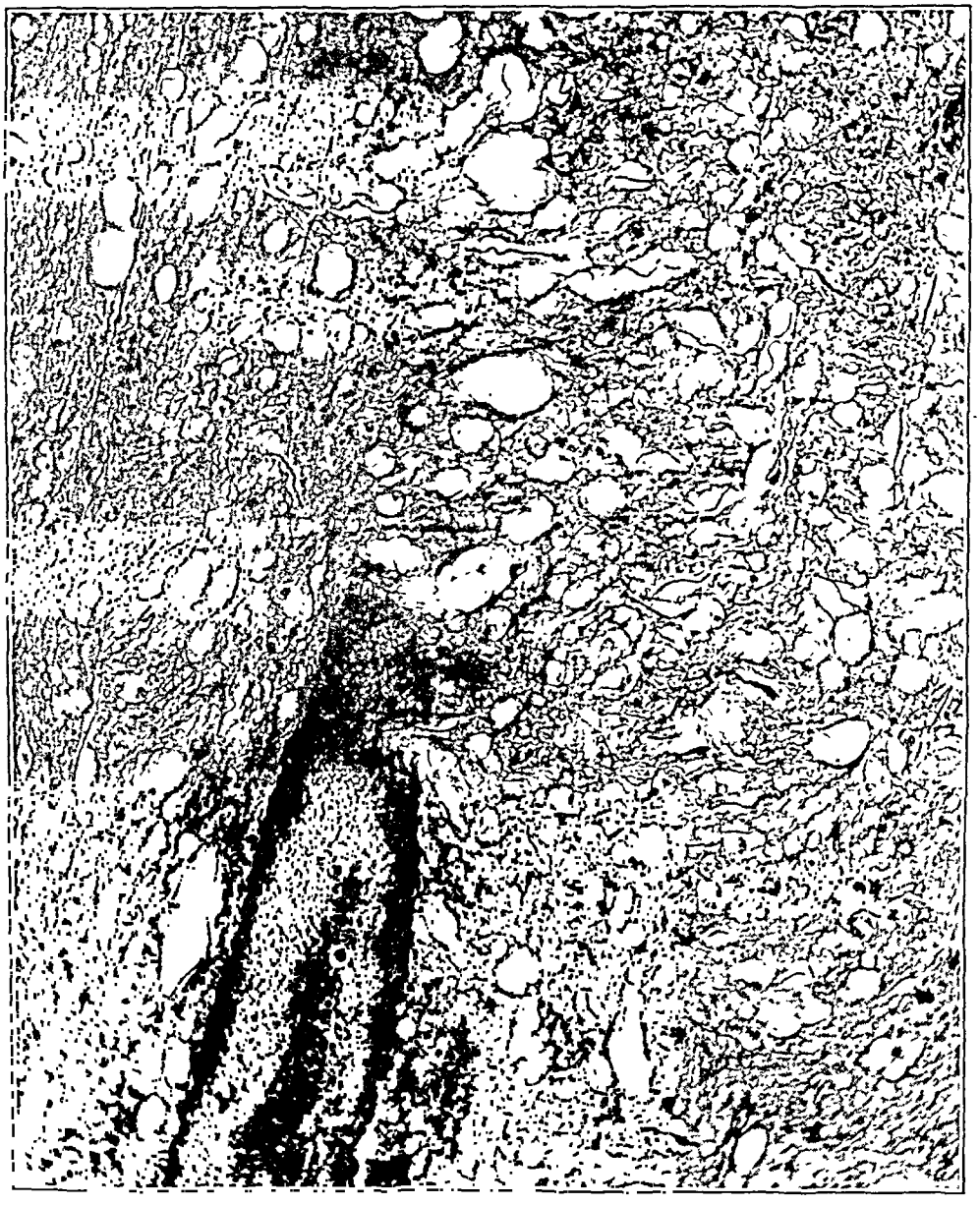

Fig. 3 (case 1).—Thrombosed vein surrounded by an area of tissue edema and necrosis. The blood clot is formed by a large mass of granular debris, fibrin threads and platelets.

cortical ribbon and the white substance. A typical picture of the distribution of the lesions in the cortex is shown in figures 4 and 5. As can easily be seen, the areas of softening occupied the entire depth of the cortical gray matter. Most of the lesions stopped abruptly before the subcortical white matter was reached; in a few instances the latter was involved to a slight extent. Occasionally there were small, disseminated foci of softening in the white matter. The pia overlying the large cortical lesions was not thickened. It contained a great number of tremendously congested surrounded by thick sleeves of gitter cells. The process described was to be seen in almost all sections taken from several areas of the frontal, the parietal and the temporal cortex. In many instances the foci of softening were chiefly limited to one cortical layer, mostly the third. Many of the foci were circumscribed and small. The majority of the small foci suggested a perivascular distribution. In the central part of the lesion one or more small veins showed changes typical of vasoparalysis (fig. 6). In addition, there were disseminated areas of circumscribed glial scar formation (fig. 7).

Examination of the subcortical white matter disclosed changes typical of far advanced edema. The tissue showed an alveolar, sievelike appearance, with formation of numerous large vacuoles separated from one another by thin trabeculae. In some an early stage of tissue liquefaction could be seen. The nerve tissue appeared cellular because of the increase of swollen oligodendroglia cells. Most of the swollen glia cells showed regressive changes in the form of ameboid transformation. The bodies of some of the cells showed increase in size and conspicuous degeneration associated with a typical picture of clasmatodendrosis, indicative of a far advanced destructive process. In addition, many veins and capillaries were tremendously distended, displaying the characteristic signs of stasis.

Sections taken from the deeper parts of the centrum semiovale exhibited a diffuse swelling of all tissue elements. In addition there was a slight degree of tissue rarefaction. The swelling of the nerve fibrils is illustrated in figure 8. There were many transitional areas between the relatively early stage of swelling of the brain and the more advanced changes described as edema.

Summary.—The most striking feature in this case consisted of numerous, diffusely circumscribed areas of softening scattered throughout the central nervous system. The lesions were characterized histologically by a patchy distribution and by an ischemic type of tissue destruction. These features suggest that the lesions were of circulatory origin, although there were no demonstrable structural changes in the vessel wall in the related meningeal and cortical vessels. Within the focal lesions the blood vessels disclosed a far advanced stage of vasoparalysis, alternating with early stages of thrombus formation.

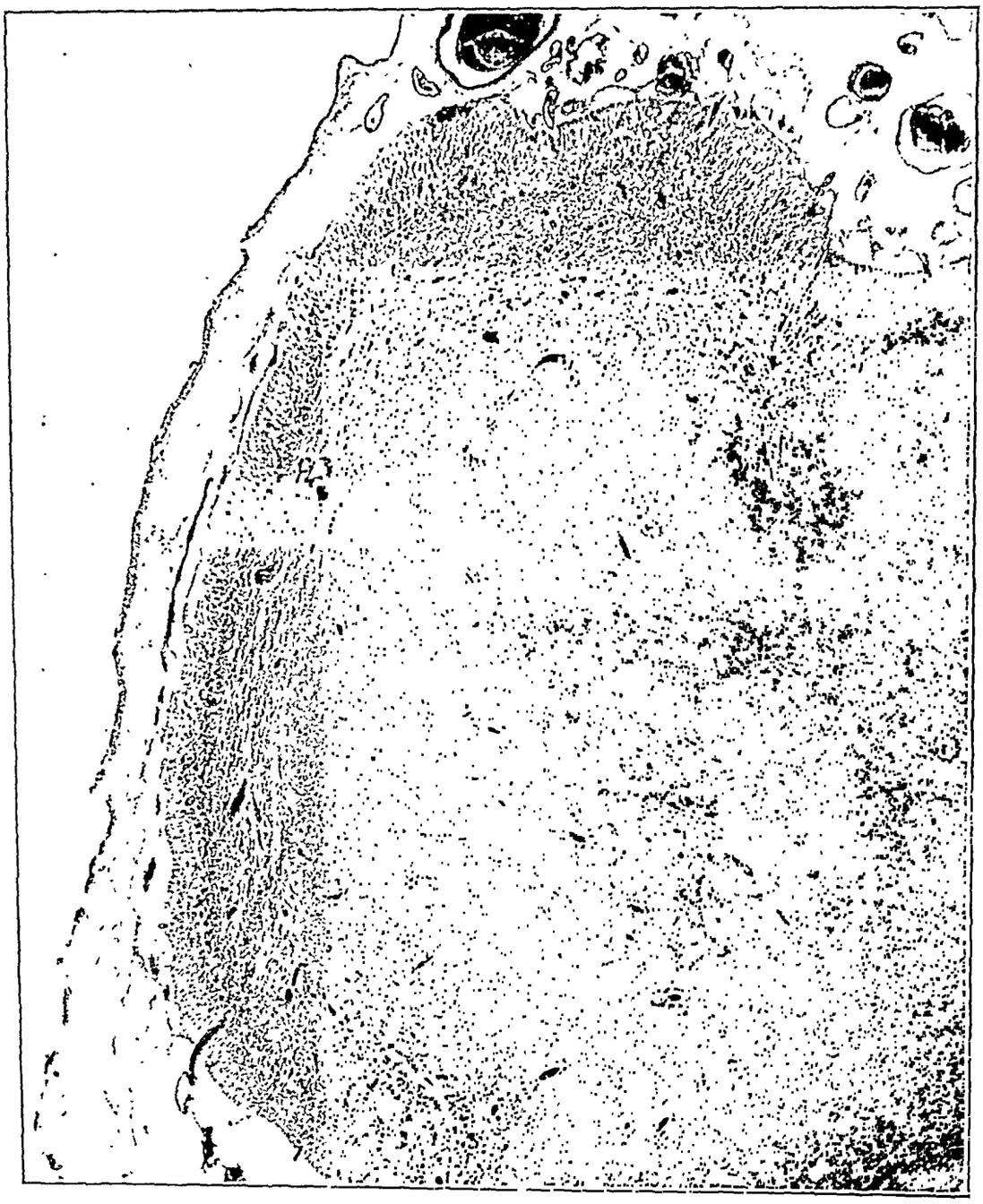

Fig. 4 (case 1).—A widely disseminated area of softening involving the cortical ribbon. Hematoxylin-eosin stain; × 35.

CASE 2.—A white man aged 63 was admitted to the hospital on June 4, 1943, with the complaint of slight clumsiness of the right arm, incoordination in walking and some delay and thickness of speech. Little in the

past history appeared to be relevant. Several weeks before his entrance to the hospital he misstepped in going downstairs and jarred himself rather severely.

On admission the temperature was 98 F., the pulse rate 68, the respiratory rate 19 and the blood pressure 220 systolic and 110 diastolic. Neurologic examination revealed that he was well developed and well nourished, but obviously dysphasic. His speech rambled, and he used improper words at times. He followed verbal commands fairly well. He had difficulty in reading headlines but was able to write to dictation fairly well

clonus bilaterally, and a questionable Babinski sign was elicited on the right. No abnormalities of coordination were detected. All forms of sensation, including position and stereognostic senses, were normal.

A lumbar puncture was performed on June 6. The *initial pressure was 75 mm. of water; the fluid was* clear and colorless and contained 3 lymphocytes per cubic millimeter and no red cells. On October 12 the patient died.

Autopsy.—Autopsy was performed two and a half hours after death. The pathologic conditions exclusive

Fig 5 (case 1) —A large area of cortical softening. Note the large number of congested and partly occluded veins. Loyez stain for myelin sheaths; × 45.

Auscultation of the head revealed nothing significant There was no evidence of head injury The visual fields and fundi were normal. The pupils were equal, each measuring 3 mm, and reacted well to light. Extraocular movements were normal. There was slight ptosis of the right eyelid The corneal reflexes were active bilaterally. There was definite weakness of the right side of the face. The appearance of the pharynx and tongue was not remarkable.

Motor power of the right arm and leg was decreased. All deep reflexes were hyperactive; there was ankle

of the lesions in the nervous system were focal myocardial fibrosis and terminal pulmonary congestion

Examination of the nervous system was limited to the brain, which weighed 1,350 Gm All the superficial veins showed diffuse congestion. The blood vessels at the base had a normal distribution and exhibited a moderate degree of arteriosclerosis. Coronal sections through both hemispheres displayed numerous, diffusely scattered areas of tissue destruction, involving both the white and the gray matter. The medulla and the pons appeared normal.

Microscopic Examination.—In general histologic examination of sections taken from various areas of both hemispheres confirmed the gross observations and revealed changes were almost identical with those described in the first case. The greater part of the cortical ribbon was "moth eaten" with numerous small areas of tissue softening. These lesions varied in size and shape; many of them were small perivascular foci restricted to an area surrounding a small vein or a group of capillaries (fig. 9). Others were somewhat larger, involving almost an entire convolution. At times they coalesced and thus assumed a pseudolaminar pattern; they produced an irregular mottled, distorted appearance of the cortical ribbon.

The histologic details were not quite uniform in all the lesions. In figure 10 is shown an area of circumscribed tissue destruction in which the entire nerve parenchyma was transformed into a large accumulation of fat granule cells. In sections stained with scarlet red, large lipid deposits were seen within the fat granule cells and in the perivascular tissue.

While these lesions represented the most frequent type of tissue destruction, focal areas of gliosis were diffusely scattered throughout the gray and the white matter. These areas were characterized by an accumulation of astrocytes and represented glial scar formation.

In almost all lesions the small blood vessels (chiefly veins) and capillaries were conspicuous because a tremendous degree of stasis and early stages of thrombus formation were present. The vascular changes were almost identical with those described in the first case; their detailed description will therefore be omitted. They are illustrated in figures 9, 10, 11 and 12. It is of interest, however, to note that thrombus formation was most frequently observed in lesions in which early changes were present; they were seldom seen in older lesions characterized by glial scar formation. The vessel wall of the smaller blood vessels did not disclose any signs of an organic vascular process. Only very few of the larger blood vessels revealed a moderate degree of arteriosclerosis.

The leptomeninges were slightly thickened and distended and contained red blood cells and gitter cells. The pial blood vessels were distended and engorged with blood and were surrounded with large accumulations of extravasated blood. Their vessel walls appeared normal.

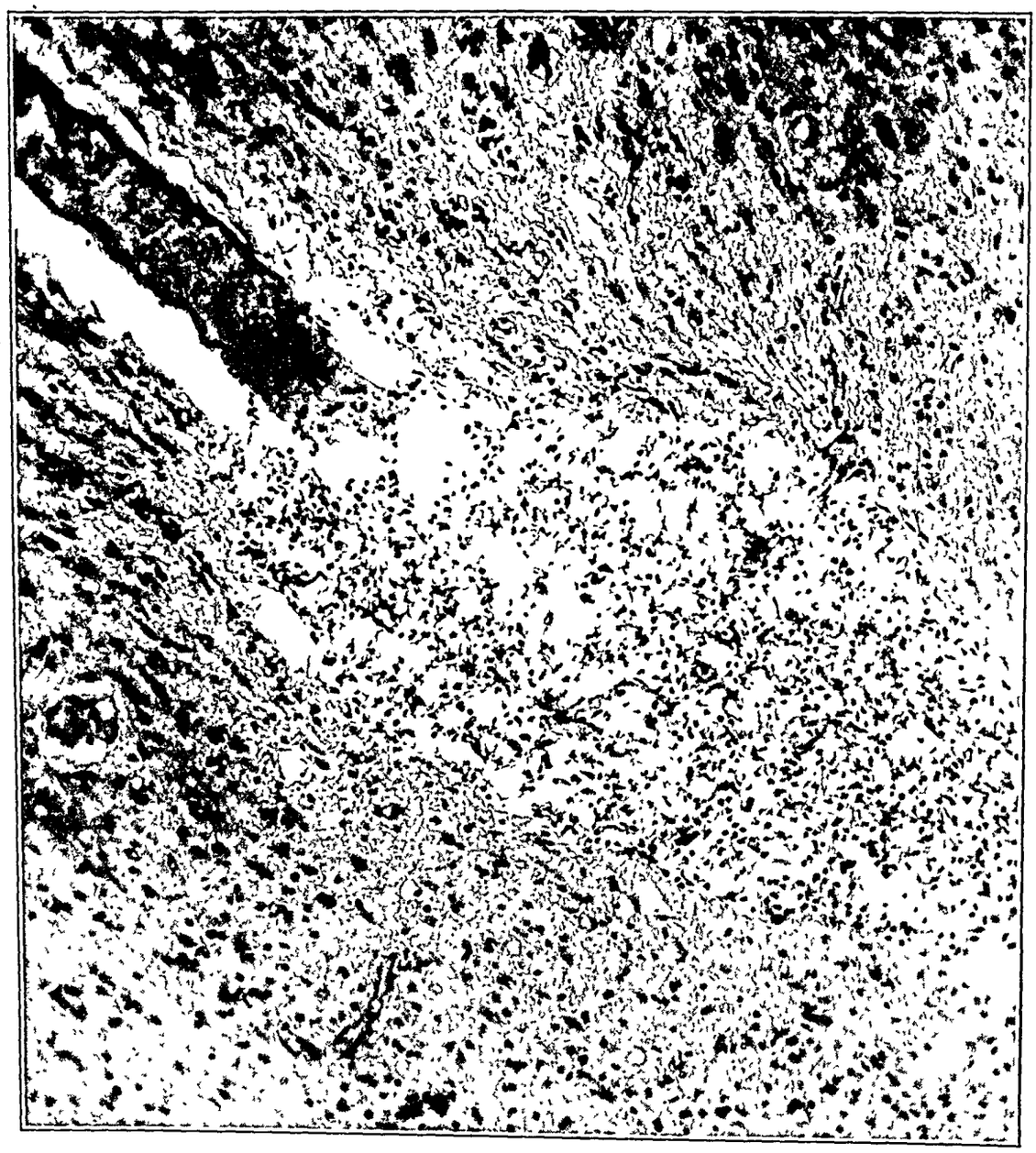

Fig. 6 (case 1).—Small circumscribed area of softening. Note the tremendously distended vein. Hematoxylin-eosin stain; × 135.

SUMMARY OF PATHOLOGIC CHANGES

The microscopic changes in both cases consisted of widely disseminated areas of softening, usually perivascular in distribution. The areas

of tissue destruction were characterized by almost complete transformation of the nerve parenchyma into compound granule cells harboring lipids and blood pigment. It should be emphasized that lack of structural changes in the vessel wall formed a striking feature of the histologic process. Neuropathologists will recognize at once that the disseminated lesions corresponded in all their details with lesions which are considered characteristic of softening of the brain tissue, of vascular origin, as frequently observed in cases of thrombosis due to arteriosclerosis, syphilis or other organic vascular disease. Attention is called to the striking fact that none of all the commonly known factors producing thrombosis could be detected. The predominant vascular alterations consisted in congestion, stasis and vasoparalysis and were associated with thrombus formation, chiefly confined to the smaller veins and capillaries. As has been demonstrated in illustrations, many of the smaller blood vessels were tremendously dilated and completely occluded with curved strands of fibrin mixed with large accumulations of platelets. In addition to the venous occlusion, histologic examination revealed in both cases a definite type of vascular alteration, which has been recently described under the heading of vasoparalysis.[2] The morphologic criteria for this vascular syndrome were listed as follows: (1) maximal distention and engorgement of the smaller veins and capillaries, (2) signs of stasis, consisting in hemolysis of red blood cells, (3) degenerative changes or complete necrosis of the vessel wall, with increased permeability for serous fluid and red blood cells and (4) distention of the perivascular spaces, which usually contain extravasated serous fluid and red blood cells.

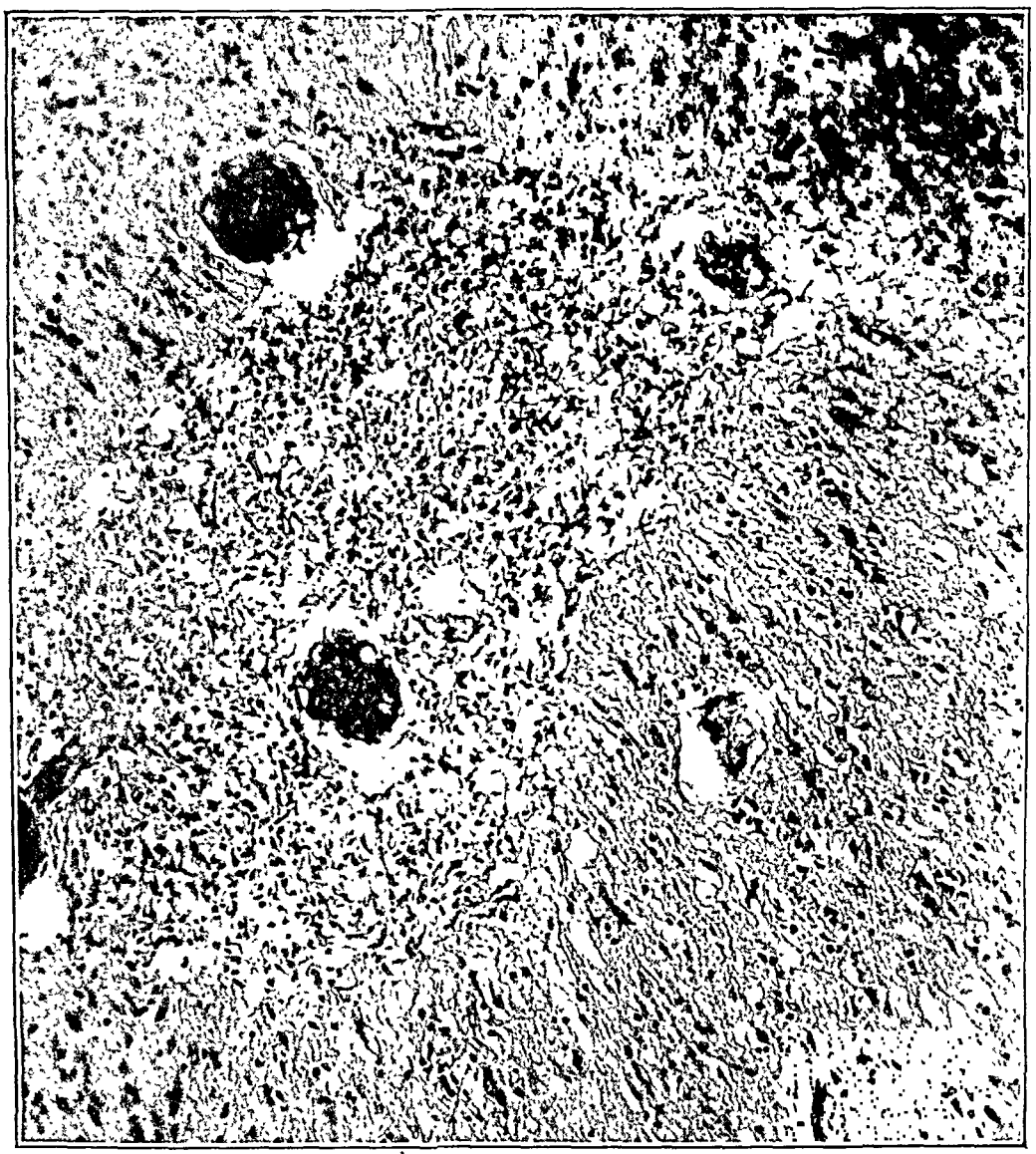

Fig. 7 (case 1).—Small area of tissue softening, with an early stage of glial replacement. Note the congested veins, with signs of vasoparalysis. Hematoxylin-eosin stain; × 135.

DIFFERENTIATION OF THE VASCULAR ALTERATIONS IN THIS SYNDROME AND THOSE IN ACUTE VASOPARALYSIS

In spite of the morphologic resemblance of the reported changes to the alterations described as characteristic of acute vasoparalysis, there were indications that some differences exist between the two conditions. These may be summarized as follows: In cases of acute vasoparalysis an increased permeability of the vessel wall for serous fluid and red blood cells, resulting in multiple petechial hemorrhages and edema, was the most striking and the predominant feature. In the vascular lesions in the cases reported here these changes were observed only occasionally and were of no great significance. The most striking feature was the presence of thrombus formation in many of the tremendously distended veins and capillaries, as illustrated in figures 2, 3, 11 and 12. Whereas the alterations in the nerve tissue in the cases of acute vasoparalysis consisted mainly of scattered small areas of petechial hemorrhages and edema, in the present cases they were represented by disseminated foci of tissue destruction consisting of recent and old areas of softening. The presence of these small foci of tissue necrosis contiguous to the occluded veins and capillaries indicates that these tissue changes were secondary to the vascular alterations.

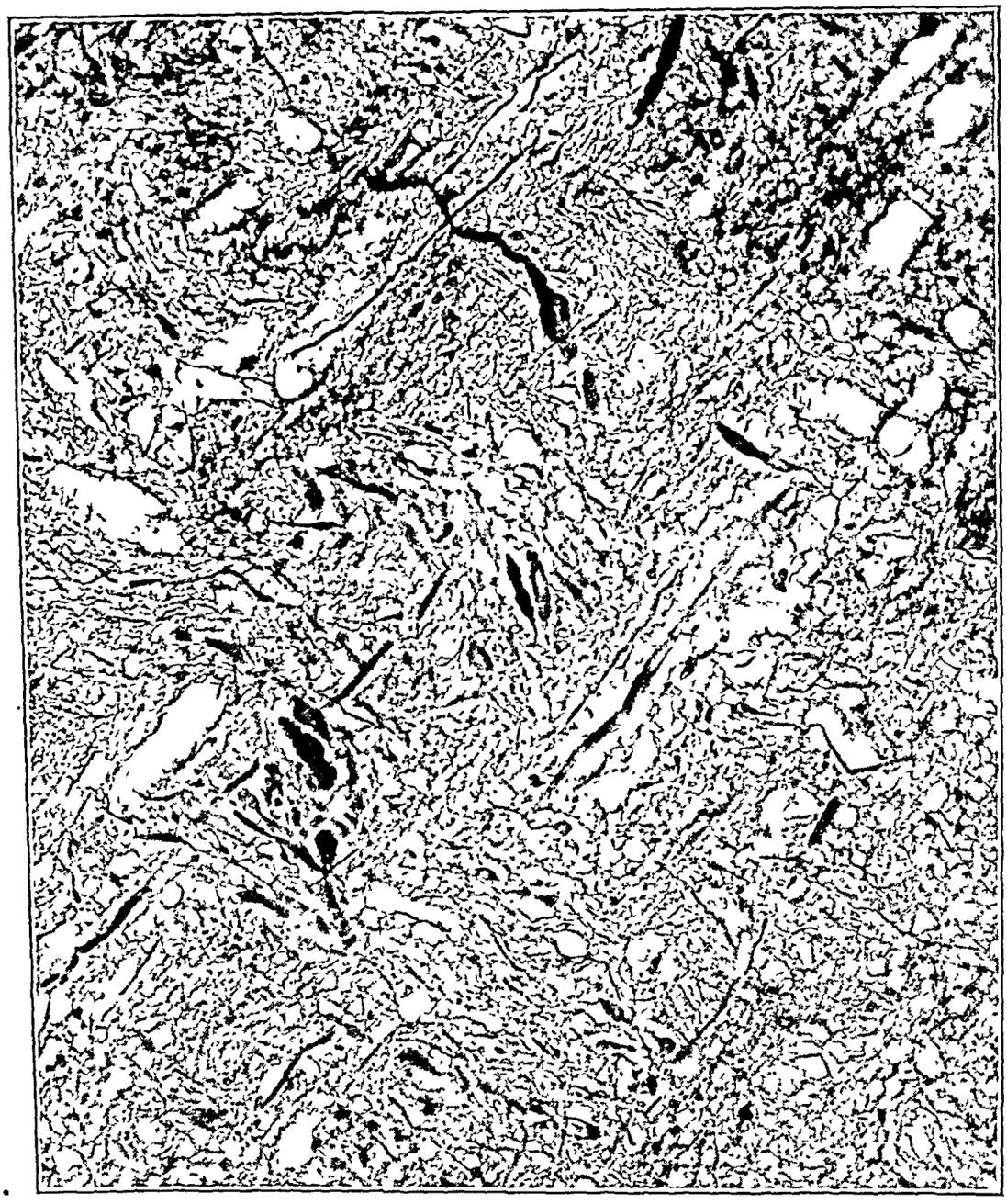

Fig. 8 (case 1).—Pronounced swelling of the axis-cylinders and tissue rarefaction. Bodian method of silver impregnation; × 225.

From these points of differentiation it seems proper to conclude that the vascular alterations under discussion should be separated from the vascular lesions of acute vasoparalysis as a special vascular syndrome, under the heading of "vasothrombosis of the central nerve system." It should be emphasized, however, that the vasothrombosis must be considered as a late sequela

of acute vasoparalysis. Both vascular syndromes, the acute vasoparalysis and the vasothrombosis, are phases of the same morbid process. The difference in their morphologic features can probably be explained by the difference in the duration and severity of the same morbid process.

DEFINITION OF VENOUS THROMBOSIS

The list of investigators who have discussed the significance of venous occlusion in disseminated sclerosis is long. There is no need to give in detail the controversy concerning this problem. My personal experience and point of view have been reported elsewhere.[3]

It is my impression that a great deal of confusion is created by the lack of a clearcut definition of the morphology of thrombosis. This is particularly true with respect to the thrombotic occlusion of smaller blood vessels, especially veins. Most descriptions in the textbooks are based on the study of thrombosis of large arteries. The morphologic feature characteristic of the occlusion of small venules is not compatible with the generally accepted conception of thrombosis of the larger arteries. The consensus among pathologists is that a pathologic state of the vessel wall caused by arteriosclerosis, syphilis or other pathologic process is necessary for the formation of a thrombus. This might be correct for the thrombotic occlusion of the smaller veins. The observations reported in this study, as well as those described by Putnam,[1]

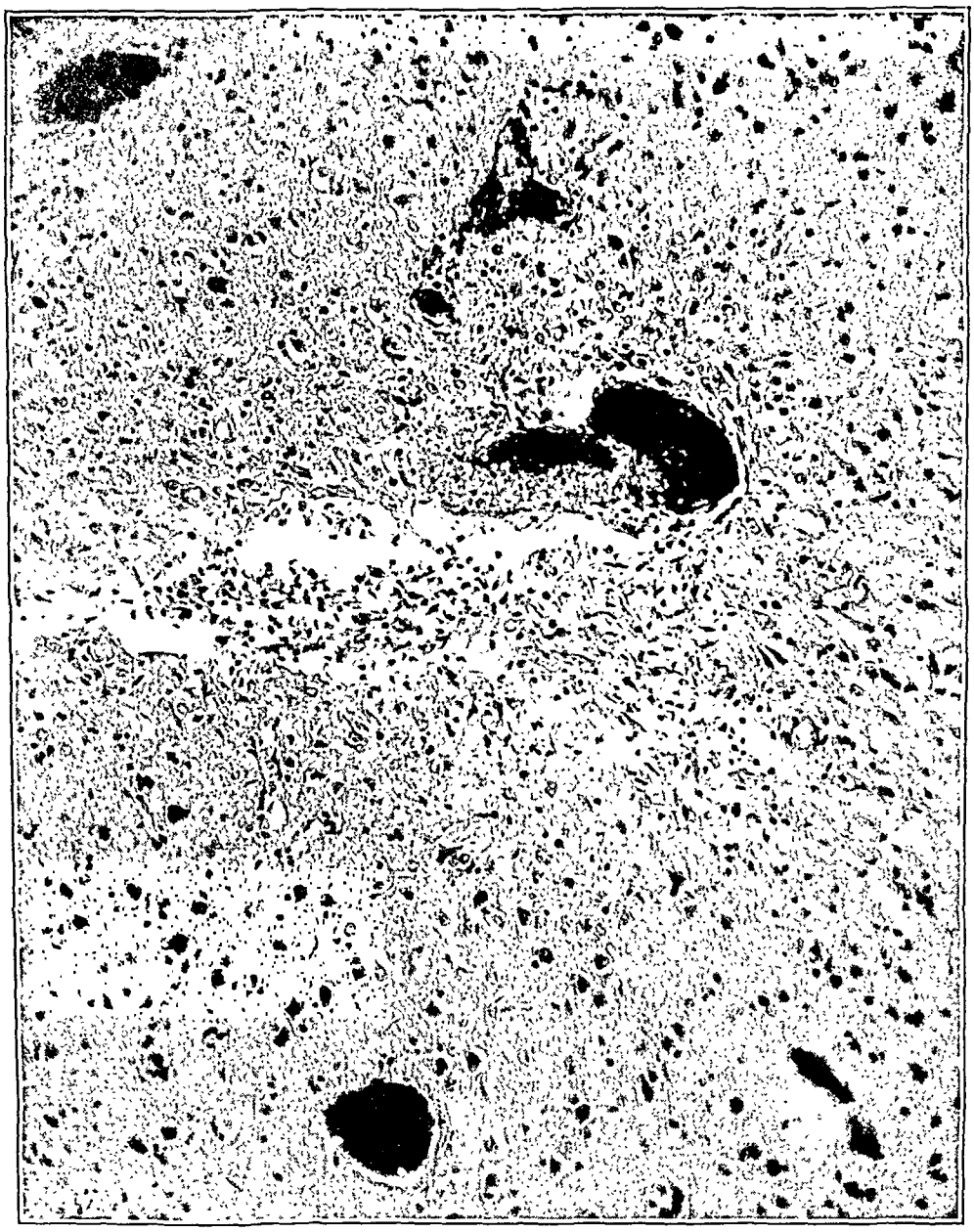

Fig. 9 (case 2).—A small area of softening in the vicinity of a vein displaying an early stage of occlusion. Hematoxylin-eosin stain; × 165.

3. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: Significance of Vascular Changes, Arch. Neurol. & Psychiat. **49**:178 (Feb.) 1943.

have demonstrated the occurrence of venous occlusion in healthy blood vessels. Recent investigations made by Stuber and Lang [4] have indicated that the production of certain chemical changes in the blood may cause clotting in intact blood vessels.

What are the morphologic criteria of venous thrombosis? In the older literature on thrombosis the chief criterion of a thrombus was the presence of an organized blood clot adherent to the vessel wall. This definition is not applicable to venous occlusion, for the following reason: As has already been stated, it is generally admitted that injury to the intima, that is, a pathologic state of the vessel wall caused by arteriosclerosis, syphilis or other organic lesion, is the main factor in the origin of arterial thrombosis. The injured intima facilitates the adherence of the blood clot to the arterial wall in the very beginning of the process. In venous occlusion the thrombus formation usually takes place in healthy vessels with a well preserved endothelial lining of the lumen. Under these circumstances adherence of the clot to the vessel wall cannot be expected, at least not in the early stage. It is therefore my impression that the mere presence of clots of an amorphous mass of agglutinated red blood cells associated with a large accumulation of platelets and large curved strands of fibrin which plug completely the lumen of an enormously distended small venule or capillary is sufficient evidence of venous thrombosis. If these changes are associated with secondary

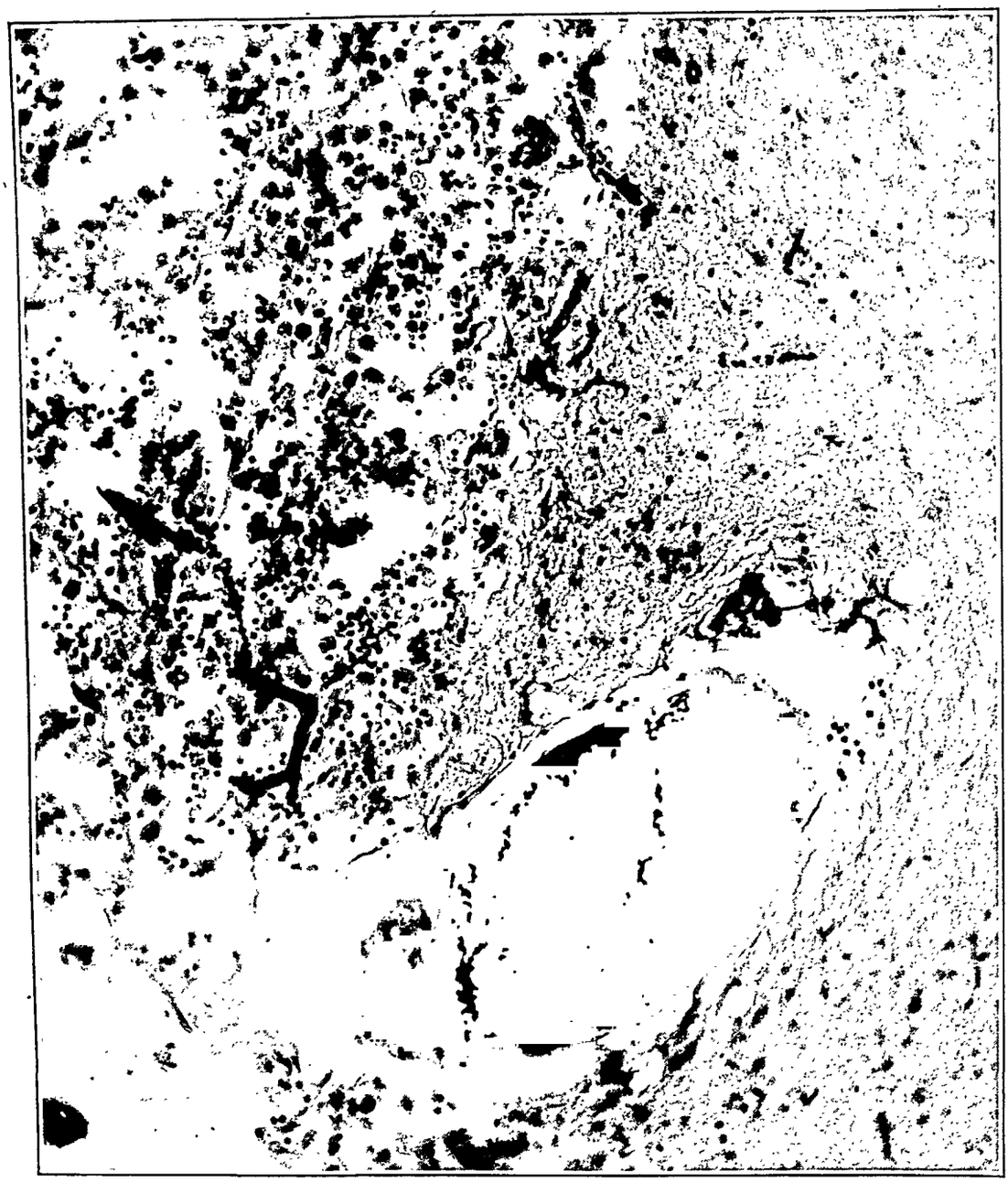

Fig. 10 (case 2).—Circumscribed area of tissue softening, with a large accumulation of fat granule cells. Note the tremendously distended and occluded vein. Hematoxylin-eosin stain; × 135.

4. Stuber, B., and Lang, K.: Die Physiologie und Pathologie der Blutgerinnung, Berlin, Urban & Schwarzenberg, 1930, pp. 74-78.

lesions of the adjacent nerve tissue, typical of vascular occlusion and perivascular in distribution, there is little doubt that the venous occlusion ought to be regarded as thrombotic. Such alterations can scarcely be confused with clot formations after death.

Of great theoretic and practical interest is the problem of subsequent development of venous thrombosis. In cases of arterial occlusion it is quite evident that within a few days or less definite signs of organization can be expected; gradual transformation into a fibrous plug, with or without final recanalization, is the usual end stage of an arterial thrombus. What is the subsequent development of a venous thrombus? According to Putnam,[1] it is conceivable that thrombosed small veins may after a certain period disintegrate completely, redissolve and be no longer recognizable. Experimental evidence for such a possibility has been given by Kusama.[5]

The fact that in my cases thrombus formation was observed mainly in early lesions and was seldom seen in foci of gliosis seems to corroborate this conclusion. The same observation was made in a study of 20 cases of disseminated sclerosis.[3] Venous occlusion was seen only in the early lesions; it was usually absent in the older, sclerotic plaques. It is therefore quite conceivable that the existing controversy concerning the presence or absence of venous occlusion in cases of disseminated sclerosis is based on the fact that the conclusions of most of the investigators were drawn from observations on old, sclerotic plaques, where the previously thrombosed veins were possibly disintegrated and no longer recognizable.

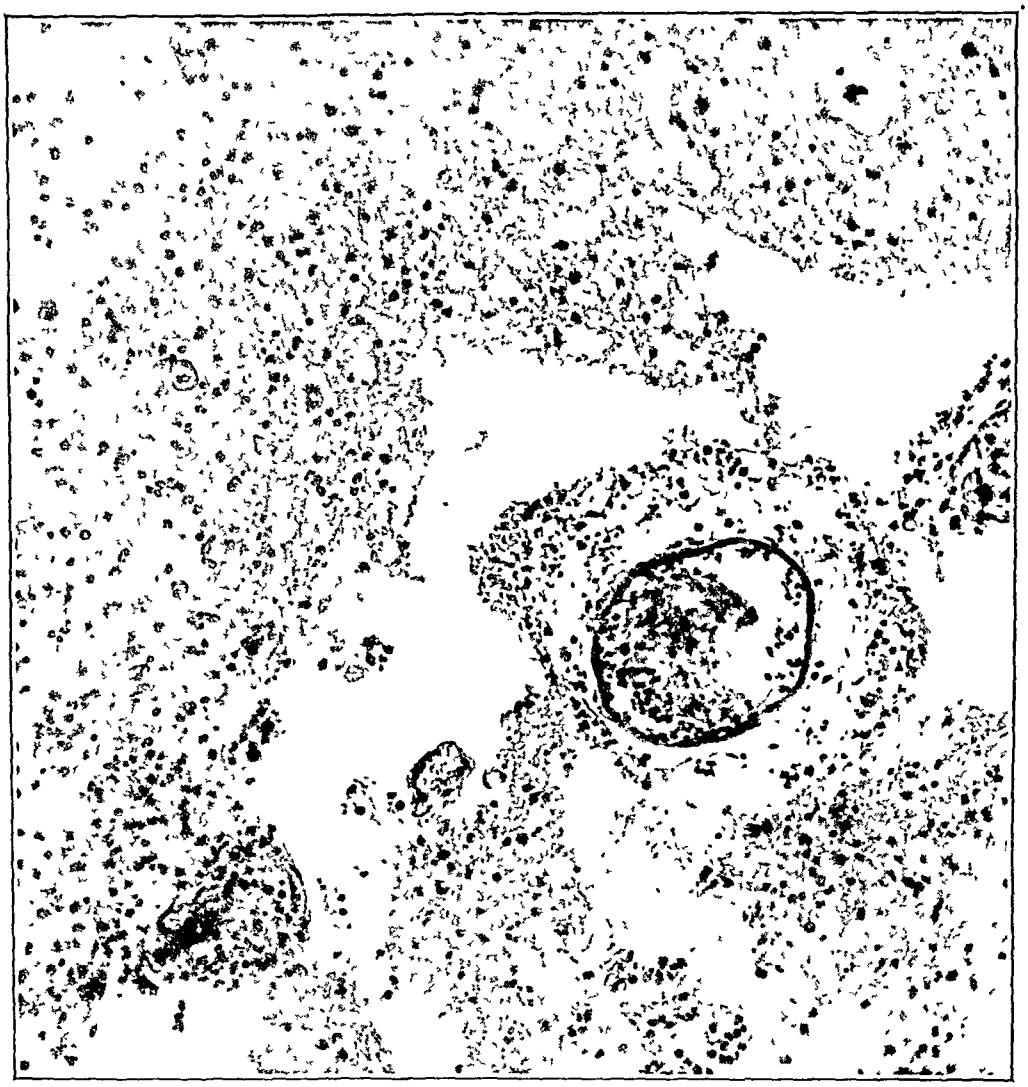

Fig. 11 (case 2).—Occlusion of a distended vein with agglutinated platelets, fibrin and blood pigment. Note the disintegration of the surrounding tissue. Hematoxylin-eosin; × 165.

TENTATIVE EXPLANATION OF THE PATHOGENESIS OF VENOUS OCCLUSION

The present study has brought out the fact that thrombus formation may develop in healthy blood vessels in which there is no indication of a primary cause of thrombosis in the vessel wall

5. Kusama, S.: Ueber Aufbau und Entstehung der toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459, 1913.

itself. Thus it would appear that the pathogenic mechanism might be expected to be present in the blood stream. What conditions in circulating blood itself or in the blood flow may lead to venous thrombosis?

According to Putnam,[1] the primary abnormal factor in venous occlusion in cases of multiple sclerosis is to be sought in the clotting mechanism of the blood.

It is my impression that the decrease in the rate of cerebral circulation ought to be considered one of the principal factors which generally favor the occurrence of venous occlusion. As has been brought out in previous papers, the state of vasoparalysis is always associated with extreme dilatation of the smaller veins and with signs of stasis characterized by hemolysis of the red blood cells. Thus, the tremendous vascular distention, together with a considerable slowing down of the blood flow, is apparently the most frequently observed factor contributing to the formation of venous thrombosis.

In support of this conception the following points may be marshaled: Zahn [6] was one of the first to demonstrate in a series of experiments that thrombosis sufficient to close the vessel occurred only in the presence of a very weak stream; in a stream of normal speed only a partial "separation" of the blood took place.

Eberth and Schimmelbusch,[7] repeating the experiments of Zahn, concluded that mechanical changes in the blood stream are as essential for thrombosis as is injury to the wall of the blood vessel. Beneke,[8] observing the streaming blood, emphasized that when partial obstruction is produced in the blood stream, there is developed peripheral to the obstruction a small whirlpool. Into this platelets are collected and held. The same phenomenon was observed when there was a sudden widening of the blood stream.

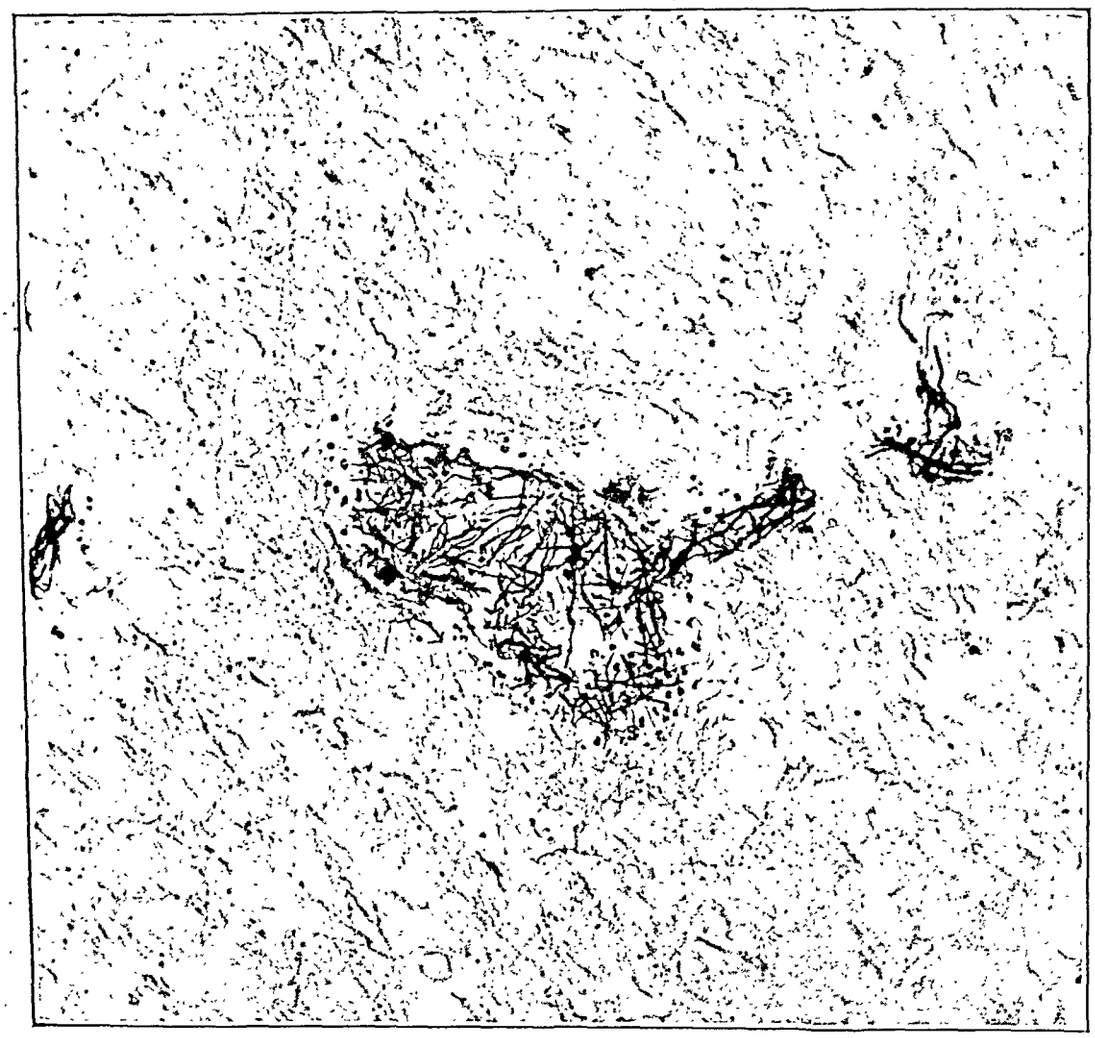

Fig. 12 (case 2).—Occlusion of a vein, with a large number of curved strands of fibrin. Phosphotungstic acid stain; ×165.

6. Zahn, W.: Untersuchung über Thrombose: Bildung der Thromben, Virchows Arch. f. path. Anat. **62**:81, 1875.

7. Eberth, J. C., and Schimmelbusch, C.: Experimentelle Untersuchungen über Thrombose, Virchows Arch. f. path. Anat. **53**:39, 1886.

8. Beneke, R., in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1913, vol. 2.

From these experimental data one may conclude that the formation of a thrombus in smaller veins may be considerably favored by partial immobilization of the blood stream.

SUMMARY

1. In 2 cases in which the smaller veins and capillaries were filled with blood clot the occlusion is interpreted as being due to local slowing down of the circulation.

2. The earliest manifestation of the pathologic process is vasoparalysis of the central nervous system.

3. The venous occlusion is apparently a late sequel of a prolonged state of vasoparalysis.

4. "Vasothrombosis" and vasoparalysis are to be considered phases of the same morbid process. The difference in their morphologic features can be explained by the difference in the duration and severity of the pathologic process.

Cincinnati General Hospital.

POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION

PATHOANATOMIC REPORT OF THREE CASES

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ANN ARBOR, MICH.

A multiple neuritis of unknown origin characterized by its frequent association with infection of the respiratory tract, increased protein in the spinal fluid without an increase in the cell content, frequent involvement of cranial nerves and a benign course was described by Guillain, Barré and Strohl[1] in 1916. The clinical distinction between this syndrome and other neuritides, frequently designated as Landry's paralysis (acute ascending myelitis), peripheral neuritis with facial diplegia, acute infective polyneuritis, acute febrile polyneuritis, infective neuronitis, acute ascending paralysis and myeloradiculitis, is not sharply defined (De Jong[2]).

No pathologic anatomy was described either in the original or in subsequent observations of Guillain,[3] who insisted on a uniformly favorable outcome as an essential diagnostic criterion. However, pathoanatomic reports with emphasis on the peripheral nervous system are available of the same disease, or at least of closely allied disorders, but little is known of the condition of the central nervous system. We wish to report 3 fatal cases of this illness with extensive changes in the spinal cord and brain stem.

REPORT OF CASES

CASE 1.—W. N., a man aged 22, a factory worker, had a sudden onset of severe abdominal pain with nausea and vomiting on Oct. 18, 1941. These symptoms were interpreted as those of appendicitis. However, appendectomy failed to bring relief; four days later, with spinal anesthesia, the entire abdominal cavity was explored, without evidence of any abnormalities. Roentgenographic and bacteriologic examinations of the gastrointestinal tract revealed nothing significant. The abdominal symptoms disappeared gradually. Five weeks later there developed a sore throat, followed by pain, weakness and numbness of all four extremities and rapid progression to complete tetraplegia. There were also transient hoarseness and weakness of the muscles of the left side of the face, with inability to close the eye. The patient was admitted to the hospital ten weeks after onset of the symptoms.

Examination.—There were bilateral paresis of the muscles of mastication; bilateral facial palsy of peripheral type, more pronounced on the left side; unilateral paresis of the recurrent laryngeal nerve; paresis of the tongue; mild dysphagia, and complete flaccid tetraplegia, with advanced muscular atrophy in all four extremities. Slight voluntary movements were preserved in the spinal, intercostal and abdominal muscles; the function of the diaphragm was normal. All superficial and tendon reflexes were absent. The sense of motion and position was lost, and vibratory sensation was diminished in all four extremities, together with distal blunting of all modalities of superficial sensation. The optic nerves, pupillary reactions, extraocular muscles and auditory nerves showed no disturbance; the muscles and nerve trunks were not tender, and signs of meningeal irritation were absent. There was an area of consolidation in the upper lobe of the right lung.

Laboratory Examination.—The urine was normal; the Kahn reaction of the blood was negative, and no Klebs-Loeffler bacilli were present on culture of material from the throat. The hemoglobin concentration was 90 per cent (Sahli); the red blood cell count was 4,900,000 per cubic millimeter; the white blood cell count ranged from 5,000 to 14,000 cells per cubic millimeter, and blood films showed no stippling of cells. The cerebrospinal fluid was under normal pressure. There were 7 cells per cubic millimeter, and the Pandy and Nonne-Apelt reactions were positive. The Kahn reaction of the spinal fluid was negative; the colloidal gold curve was 0001221100, and the total protein content was 400 mg. per hundred cubic centimeters. Blood cultures yielded no growth; no lead or abnormal pigments were found in the urine. Roentgenograms revealed an abscess in the upper lobe of the right lung.

Course in the Hospital.—The pulmonary infection grew steadily worse, and the patient died eighty-five days after onset of the neurologic symptoms.

Pathoanatomic Examination.—Peripheral Nerves: There was advanced degeneration of the myelin sheaths, numerous bundles of which had lost their normal structure and appeared almost amorphous in azan preparations; such bundles were greatly swollen, their diameter being five to six times that of the normal. The axis-cylinders were swollen and fragmented, and their number was greatly reduced. The Schwann cells were increased in size and number. Marchi preparations contained numerous myelin fragments (fig. 1).

Read at the Seventieth Annual Meeting of the American Neurological Association, New York, May 20, 1944.

From the Neuropathology Laboratory of the Neuropsychiatric Institute, and the Department of Neurology, University Hospital and the University of Michigan Medical School.

1. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbumose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462 (Oct. 13) 1916.

2. De Jong, R. N.: The Guillain-Barré Syndrome, Arch. Neurol. & Psychiat. **44**:1044 (Nov.) 1940.

3. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

Posterior Root Ganglia: The parenchymal cells of the peripheral ganglia showed outspoken axonal degeneration (fig. 2).

Central Nervous System: Most information was obtained from the Marchi sections, which demonstrated severe degeneration of the white matter in all columns of the spinal cord and in numerous systems as far as the thalamus. The fasciculus gracilis and fasciculus cuneatus were laden with Marchi bodies (fig. 3). There was also severe degeneration of the spinocerebellar pathways and the pyramidal and rubrospinal tracts. The same picture prevailed throughout the spinal cord and continued into the medulla. The fibers of the medial lemniscus contained large masses of myelin fragments, so that the bundles were sharply outlined (fig. 4); the fibers of the hypoglossus nerve stood out distinctly, being heavily laden with myelin fragments (fig. 4). There were similar severe changes in the olivocerebellar fibers and in the fibers of the reticulate substance, as well as in the intrabulbar portion of the fibers of the fifth, eighth, ninth and tenth nerves. The degeneration was less severe in the tectospinal tract and in the medial longitudinal fasciculus. The external arcuate fibers were not degenerated.

In Nissl preparations axonal degeneration was outspoken in the lumbar and sacral segments of the cord, particularly in the dorsolateral nuclei of the anterior horns; shrunken, deeply staining neurons could be seen in the higher segments of the spinal cord and in the brain stem as far as the midbrain. The basal ganglia, the cortex, the cerebellum and the meninges showed no pathologic changes.

Fig. 1.—Photomicrograph of section of a peripheral nerve, showing numerous fragments of degenerated myelin (black). Marchi method; Zeiss planar lens, 20 mm.

CASE 2.—E. P., a truck driver aged 21, was admitted to the University Hospital on March 28, 1941. Three weeks previously he noted numbness in the feet, which soon became paralyzed, progressive weakness in the hands, double vision and pain in the back of the head. There was no history of antecedent infection.

Examination.—Examination revealed paralysis of the left lateral rectus muscle and palsy of the left side of the face of peripheral type; flaccid tetraparesis with proximal predominance; bilateral diminution of the biceps reflex, with absence of the remaining deep tendon reflexes; normal cremasteric and abdominal reflexes, and an extensor plantar response on the right side, with an equivocal extensor plantar response on the left side. There were mild dyspnea, dysarthria and dysphagia, mild paresis of the abdominal and intercostal muscles and moderate paresis of the deep spinal muscles. Vibratory sensation and the sense of position were notably diminished in the lower extremities and moderately diminished in the upper extremities. Superficial sensation was preserved except for diminished pain and tactile sense in a radicular pattern corresponding to the upper lumbar dermatomes. The muscles and nerve trunks were tender to palpation, and there were mild nuchal rigidity and a faint Kernig sign.

Laboratory Examinations.—The urine was normal. The Kahn reaction of the blood was negative. There were 14,000 white blood cells per cubic millimeter, with variations from 6,000 to 22,000 cells. The blood was otherwise normal. The cerebrospinal fluid was clear and colorless, contained no cells and was under normal pressure; the Kahn reaction of the fluid was negative, and the colloidal gold curve was normal. The Pandy and Nonne-Apelt reactions were positive; the total protein content was 105 mg. per hundred cubic centimeters.

Course in the Hospital.—Increasing weakness of the respiratory muscles complicated with pneumonia required treatment in the Drinker respirator from the third to the twenty-fourth day of hospitalization. The pneumonia responded to treatment with sulfadiazine and oxygen, and the patient was removed from the respirator. However, twelve days later the respiratory difficulties increased; the pulmonary infection became grave, and death occurred on the sixty-fifth day after the onset of the symptoms.

Pathoanatomic Examination. — Peripheral Nerves: Degeneration was of the same type as that in the preceding case.

Posterior Root Ganglia: There was outspoken axonal degeneration.

Central Nervous System: Marchi preparations disclosed large accumulations of black myelin fragments in the white matter of the spinal cord, particularly in the fasciculus gracilis and fasciculus cuneatus (fig. 5).

the function of the diaphragm was normal. Vibratory sensation was absent at the ankles and wrists; the sense of position was absent in the toes and impaired in the fingers, and there was distal blunting of all modalities of superficial sensation to the midthigh in the lower extremities and to the elbows in the upper extremities. All active and passive movements were painful, and there were severe generalized tenderness of the muscles and mild nuchal rigidity. The optic disks, the reactions of the pupils, the extraocular movements and the function of the muscles of mastication and of the sphincters were normal.

Laboratory Examination.—The Kahn reaction of the blood was negative, and urinalysis showed nothing abnormal. There were 14,800 white blood cells per cubic millimeter, of which 81 per cent were polymorphonuclear leukocytes. The cerebrospinal fluid was clear and faintly xanthochromic and contained 5 lymphocytes per cubic millimeter; it was under a pressure of 60

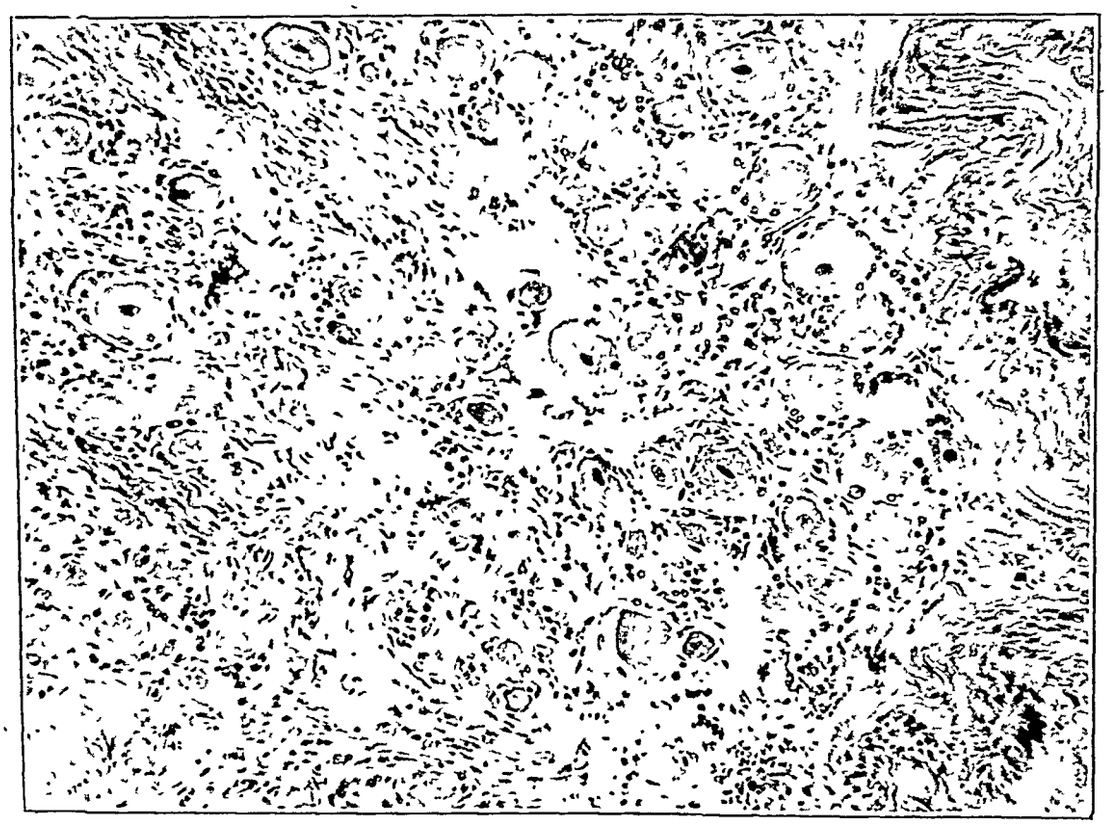

Fig. 2.—Photomicrograph showing axonal degeneration (posterior root ganglion). Azan stain; objective (Zeiss) × 20; ocular, projection 2.

The parenchyma showed a variety of degenerative changes. There was outspoken axonal degeneration in the lumbosacral segments, but not elsewhere in the central nervous system. In the higher segments of the cord, the medulla and the midbrain, the dominant change was shrinkage of the neurons, which in Nissl preparations stained a deep blue. The glia remained inactive. The basal ganglia, cortex, cerebellum and meninges were normal.

CASE 3.—S. Z., a girl aged 19 years, had coryza and a cough, followed by pain in the back, numbness and progressive weakness of all the extremities eight days before her admission to the hospital.

Examination.—There were bilateral facial paralysis of peripheral type, mild paresis of the uvula and tongue, mild dyspnea, dysarthria, dysphagia and flaccid tetraplegia, with absence of all deep and superficial reflexes. The paralysis was complete in the lower extremities and nearly complete in the upper extremities, where it was without definite proximal or distal predilection. There was moderate paresis of the deep spinal, the abdominal and the accessory respiratory muscles, but

mm. of water, and there was no manometric block. The Kahn reaction of the cerebrospinal fluid was negative; the colloidal gold curve was 1144433221; the Pandy and Nonne-Apelt reactions were positive, and the total protein content was 1,333 mg. per hundred cubic centimeters. A pellicle formed on the fluid's standing. Cultures of the spinal fluid yielded no growth, and attempts to isolate a virus by chick embryo culture and intracerebral inoculation of mice were unsuccessful.

Course in the Hospital.—Ten days after admission increasing paralysis of the respiratory muscles required the use of a Drinker respirator, in which the respirations improved temporarily. On the sixteenth day of illness pneumonia developed, and the patient died three days later. The temperature was normal until the onset of pneumonia; the pulse and respiratory rates were continuously elevated, the rates varying with the degree of respiratory distress. The duration of the disease was twenty-one days.

Pathoanatomic Examination. — Peripheral Nerves: The axis-cylinders were greatly swollen, appearing six

or eight times as thick as normal, and seemed to compress remnants of degenerated myelin. The latter was broken down into small fragments, which filled the perineural sheaths in a disorderly manner; the Schwann cells were proliferated, and their nuclei were swollen; there were occasional gitter cells; the perineural tissue was moderately increased.

Posterior Root Ganglia: The neurons showed advanced axonal degeneration and were greatly swollen; their tigroid substance was destroyed, and the nuclei were shrunken or no longer visible.

Central Nervous System: There was advanced axonal degeneration in the lumbosacral segments, while in the thoracic and cervical segments the neurons were shrunken, staining a homogeneous deep blue. In the midbrain, the basal ganglia and the cortex of both hemispheres the neurons stained pale blue, the tigroid substance appearing dustlike, or not being visible at all. Marchi preparations showed numerous myelin fragments in the white matter of the thoracic, lumbar and sacral segments of the spinal cord. Unfortunately, no Marchi preparations were available from segments above the upper thoracic level. The meninges and cerebellum appeared normal.

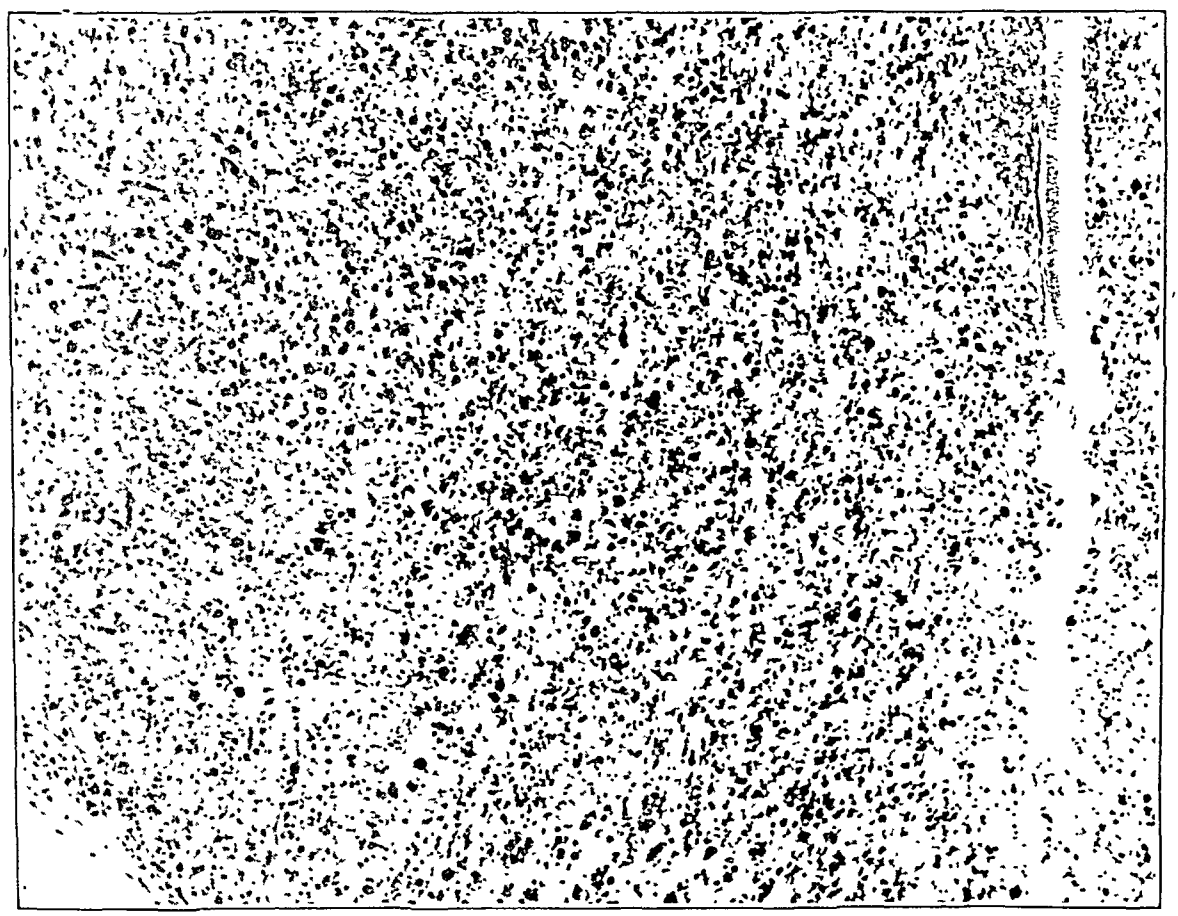

Fig. 3.—Fasciculus gracilis and fasciculus cuneatus with numerous degenerated myelin fragments (upper lumbar cord). Marchi method; Zeiss planar lens, 20 mm.

COMMENT

Although it is the consensus that in the Guillain-Barré syndrome [1] the peripheral nerves regularly undergo severe degeneration, little is known of the pathoanatomic changes in the central nervous system. Most authors reported either no changes at all or alterations of a mild or reversible nature. Only in 3 cases has definite degeneration been observed. In these cases the clinical course was protracted (seven and a half, ten and nineteen months respectively), and the degeneration was restricted to the posterior columns of the spinal cord (Russell and Moore [4]; Gilpin, Moersch and Kernohan [5]) and the dorsal spinocerebellar tracts (Shaskan, Teitelbaum and Stevenson [6]).

As our observations show, the central nervous system may undergo extensive and fatal damage to its myelin and parenchymal cells in the early acute stages of the disease; these changes are degenerative and stimulate only a limited cellular response. Even in the peripheral nerves, which possess a powerful regenerative capacity, the cellular activity remains restricted to moderate

4. Russell, W. D., and Moore, W. L.: Permanent Damage to the Nervous System Following an Attack of Polyradiculoneuritis (Guillain-Barré Syndrome), Arch. Neurol. & Psychiat. **49**:895 (June) 1943.

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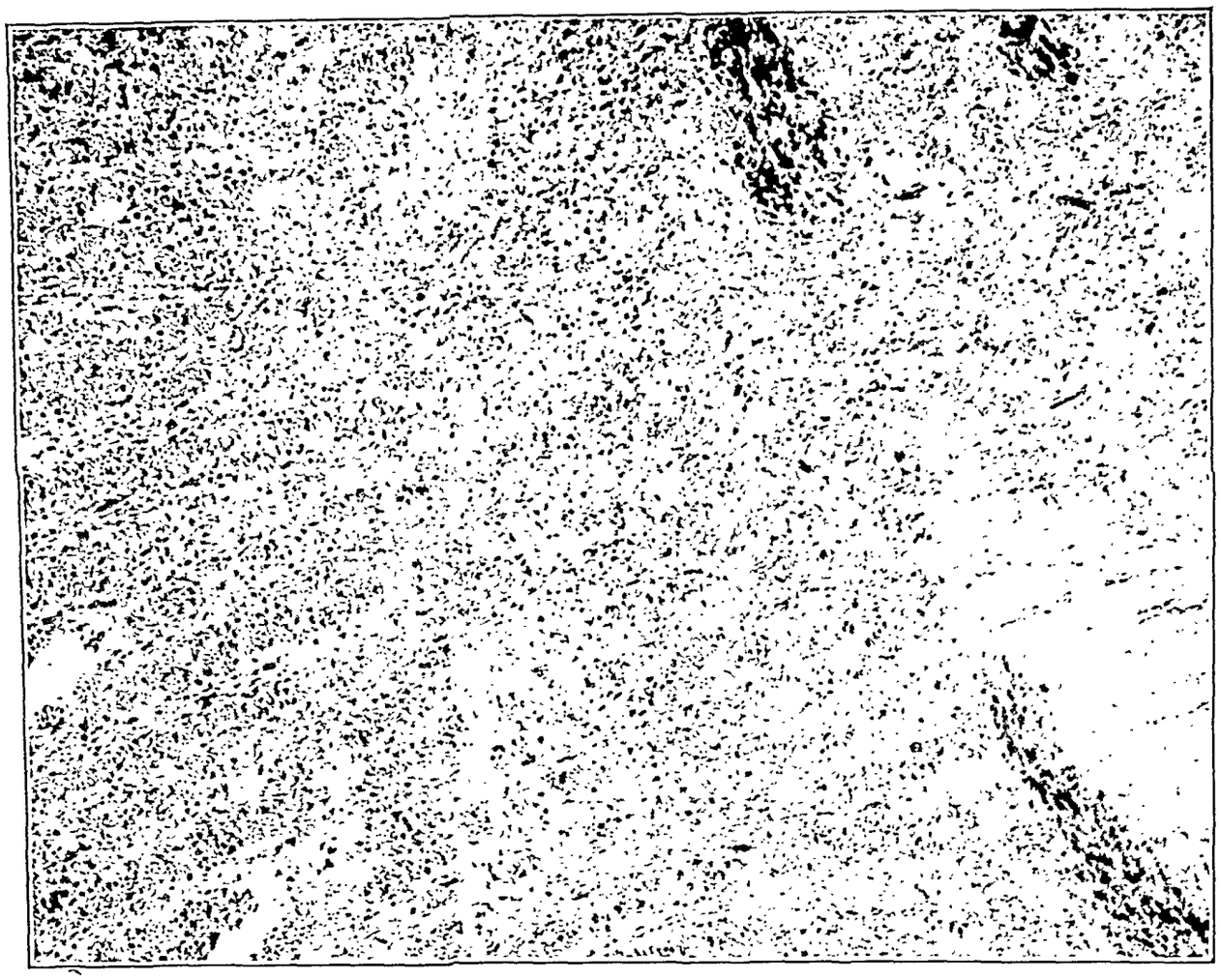

Fig. 4.—Section through the medulla at the level of the twelfth nerve, showing advanced degeneration of the myelin in the medial lemniscus, the fibers of the hypoglossus nerve and the reticular substance. Marchi method; Zeiss planar lens, 20 mm.

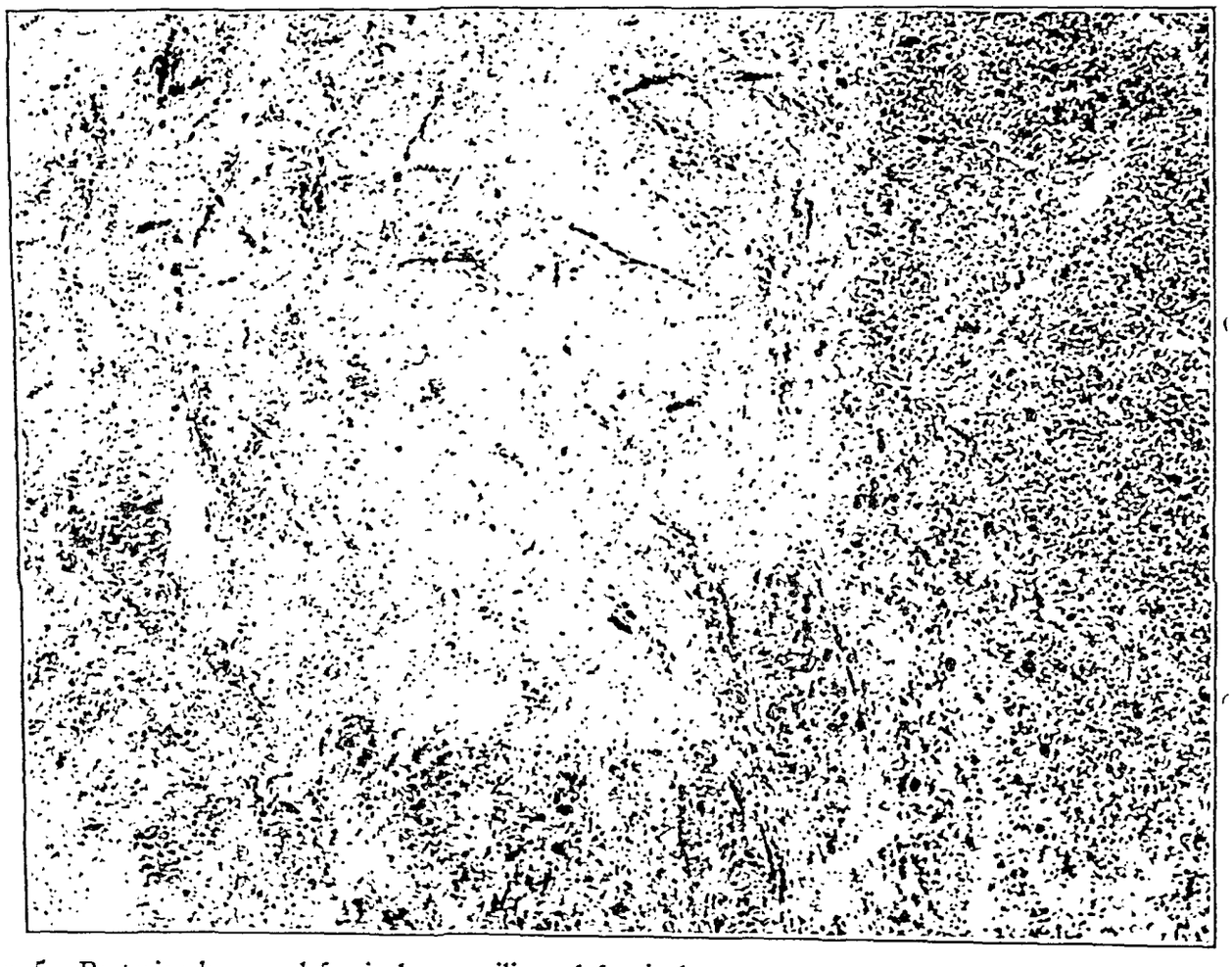

Fig. 5.—Posterior horn and fasciculus gracilis and fasciculus cuneatus laden with numerous myelin fragments (lumbar portion of cord). Marchi method; Zeiss planar lens, 20 mm.

proliferation of the Schwann elements and of the perineural connective tissue. This lack of cellular reaction is even more striking in the central nervous system, where the regenerative power is negligible, a condition which accounts for the frequently reported failure of cellular preparations to demonstrate definite changes. The histologic analysis is rendered still more difficult by lack of demonstrable signs of lipid degeneration in scarlet red and Weigert preparations, which in cases of this disorder give positive results only with the chronic form. In all 3 of our cases of the acute form both these methods failed to yield conclusive results.

In our opinion the character and the full extent of the pathoanatomic changes in the acute stage of the disease can be demonstrated only by the Marchi method, since in our cases this technic showed extensive degeneration not only in the peripheral nerves but in the white matter of the spinal cord and of the brain stem. Unfortunately, we were not able to employ this technic at levels higher than the midbrain, so that the full extent of the degeneration remained unknown. We were able, however, to trace it through the medial lemniscus, which suggests that the morbid process reached at least the level of the thalamus.

Degeneration of the parenchyma occurs regularly, but it seems to be secondary to degeneration of the myelin and its extent varies. Three histologic types may be distinguished. The most conspicuous type is that of axonal degeneration: It was regularly seen in the posterior root ganglia and in the lumbosacral segments of the cord, but occurred in few cells at higher levels. This type of degeneration has considerable differential value. It was noted by Spielmeyer [7] in cases of polyneuritis associated with so-called Landry's paralysis. This we can confirm: In 7 cases of the latter syndrome available in this laboratory axonal degeneration was constantly present in the lumbar segments, its presence suggesting a possible pathoanatomic relation, at least in some cases, between the Guillain-Barré [1] syndrome and the disturbance diagnosed as Landry's paralysis.

Less conspicuous than the axonal degeneration, but much more widespread, is shrinkage of the neurons, which stained a deep blue in Nissl preparations. These cells could be seen throughout the spinal cord and the brain stem. This type apparently represents a degenerative phase preceding axonal degeneration, since both processes were frequently present in the same nucleus.

The third type of parenchymal degeneration was noted in case 3, in which the neurons stained poorly and appeared pale. This change was universal, affecting also the basal ganglia and the cortex of both hemispheres. It is possibly toxic. Its true nature and significance remain obscure, but its severity corresponded to the stormy clinical course.

Little is known of the involvement of the autonomic nervous system. Clinical manifestations in some cases indicate a possible implication early in the course of the disease. Abdominal symptoms without a demonstrable anatomic basis were present in the case of Russell and Moore [4] and in our case 1. Pathoanatomic changes were reported by Roseman and Aring,[8] who noted degenerative changes in the sympathetic ganglia, and by Paliard and Dechaume,[9] who observed lymphocytic infiltration and an increased number of satellite cells in the solar plexus.

SUMMARY

It may be stated that the uniformity of the clinical and pathoanatomic observations suggests that the disorder represents a disease entity rather than a syndrome. It is characterized by primary degeneration of the myelin in the peripheral nerves, spinal ganglia, cord and brain stem. The equally severe involvement of efferent and afferent pathways and the disregard for synapses exclude the possibility of secondary degeneration within the central nervous system arising from primary disease of the peripheral nerves.

The cause remains obscure; attempts in our cases to recover a "virus" from the spinal fluid or from suspensions of nerve tissue were unsuccessful.

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LESIONS IN THE BRAIN ASSOCIATED WITH MALARIA

PATHOLOGIC STUDY ON MAN AND ON EXPERIMENTAL ANIMALS

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Pathologic changes in the brain frequently are noted in patients who have died of malaria. Petechiae in the meninges and the brain tissue are probably the lesions most often observed. Gaskell and Millar [1] stated that these hemorrhages resulted primarily from degeneration of the endothelial cells lining the capillaries. Other investigators have expressed the opinion that red blood cells accumulate along the injured capillary walls and hinder the exchange of nutritive materials.[2] Occlusion of the cerebral capillaries by thrombi composed of parasitized erythrocytes is considered usually to be the basis for the development of the hemorrhages. Laveran [3] was one of the first to claim that these hemorrhages developed from thrombi.

Cellular reactions within the brain substance and in the meninges also have been described in cases of malaria.[4] Malarial nodules have been observed in the subcortical areas of the cerebrum and infrequently in the cerebellum.[4] Margulis [5] apparently was one of the first to describe this lesion. He suggested that it resulted from stasis and thrombosis of the neighboring capillaries since it was frequently associated with hemorrhages. Dürck [6] described a similar lesion unassociated with hemorrhages and expressed the opinion that it developed as the result of the action of malarial toxin on the capillaries and on the brain tissue. These granulomatous nodules in the brain are usually referred to in the literature as "Dürck granulomas." Both Dürck [6] and Thomson and Annecke [4] discussed the pathogenesis of this lesion.

Degenerative lesions in the cells of the brain were described by Marchiafava and Bignani [7] as early as 1890. They reported the presence of chromatolysis in large nerve cells, accompanied by other degenerative changes. Lafora [8] also described chromatolysis, swelling and vacuolation of the cytoplasm, loss of Nissl granules and degeneration of the medullated fibers in the brain of patients who died of the malignant types of malaria.

A variety of clinical manifestations have been observed in patients with acute and chronic malaria.[9] De Vries [10] reported a case of cerebellar ataxia with hyperactive tendon reflexes, tremor, slurring speech and nonconvergence of the eyes. Simpson and Sagehiel [9c] reported a case of malaria in which there were manifestations of a cerebellar syndrome, with weakness, ataxia and dysmetria of the extremities. Cerletti [11] emphasized the frequence with which

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9. Masson, C. B.: Effects of Malaria on the Nervous System with Special Reference to Malarial Psychoses, Am. J. M. Sc. **168**:334-371, 1924. (*b*) Turner, C. C.: The Neurologic and Psychiatric Manifestations of Malaria, South. M. J. **29**:578-586, 1936. (*c*) Simpson, W. M., and Sagehiel, J. L.: Cerebral Malaria, U. S. Nav. M. Bull. **41**:1596-1602, 1943.

10. de Vries, E.: Nervous Complications in Pernicious Malaria, China M. J. **41**:503-508, 1927.

11. Cerletti, U., 1909, cited by Thomson and Annecke.[4]

a cerebellar syndrome occurred in cases of malaria. Deaderick,[12] however, expressed the opinion that symptoms originating from the cerebellum were present only in rare instances. Neurologic lesions have been observed infrequently in experimental animals. Simpson,[13] in June 1944, described them in a turkey infected with Plasmodium durae. He stated:

This animal seemed to be partially paralyzed for several hours before its death, and although it was able to flap its wings, it could not raise its head or stand on its legs.

METHODS AND MATERIAL

The material used in this study consisted of the brain of a child who died in the acute stage of infection with Plasmodium falciparum, the brains of 3 monkeys infected with Plasmodium knowlesi and the brains of a series of ducks and chicks infected with Plasmodium lophurae.

The human brain was removed within three hours after death. Two of the monkeys were perfused with a 10 per cent concentration of solution of formaldehyde U. S. P. immediately after they were bled to death.

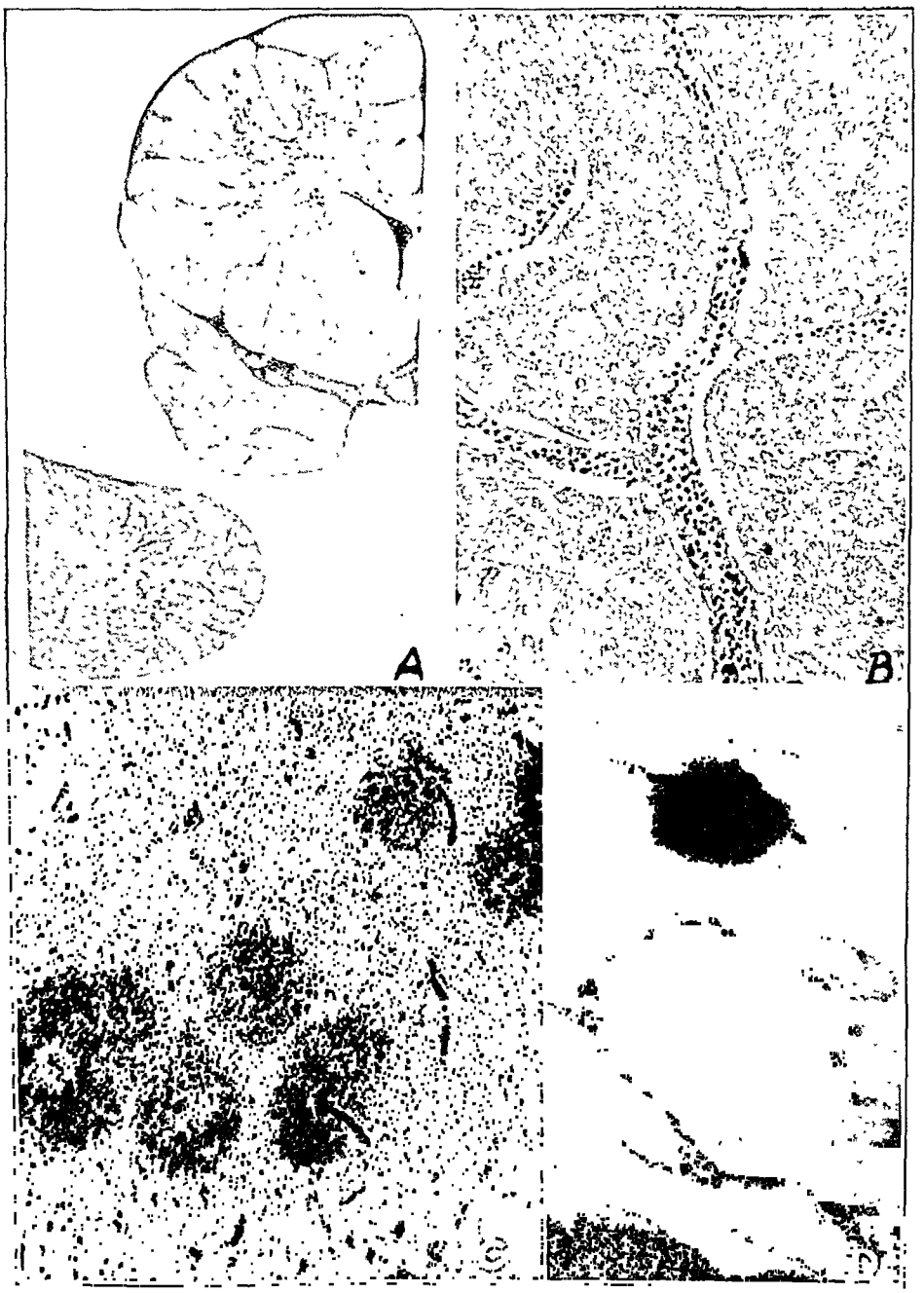

Fig. 1.—Petechiae in the brain of a child aged 7 years who died of infection with P. falciparum. *A*, petechiae in the cerebral hemisphere and cerebellum. *B*, parasitized erythrocytes filling the lumen of a blood vessel. A hemorrhage has occurred around this vessel. Hematoxylin and eosin; × 430. *C*, petechiae associated with capillaries. The red cells may form the ring type of hemorrhage. Hematoxylin and eosin; × 100. *D*, capillaries throughout the brain filled with parasitized cells. The petechiae here appear as black areas. Tissue cleared in alcohol, benzine and methyl salicylate; × 100.

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The brain from the third monkey was obtained within thirty minutes after death by bleeding. The brains from the ducks and chicks were removed at varying intervals after the intravenous injection of P. lophurae. A cervical clamp was applied, and the brain was removed and placed in the fixative within one minute.

The following fixatives were used: a 10 per cent concentration of solution of formaldehyde U. S. P., 95 per cent alcohol; Zenker's fluid, and Bouin's solution. Paraffin sections and the following staining technics were used: hematoxylin and eosin, 0.5 per cent thionin, Weil's iron hematoxylin stain for myelin sheaths, osmic acid and scarlet R for fat and Bodian's and Bielschowsky's silver technics.

The ducks used in this study usually had a high degree of parasitemia such that approximately 90 per cent died during the early stage of the infection. Of the remaining 10 per cent, all manifested clinical neurologic signs within two to eight weeks. In this study we used only brains of birds that were killed at varying intervals during the course of the disease.

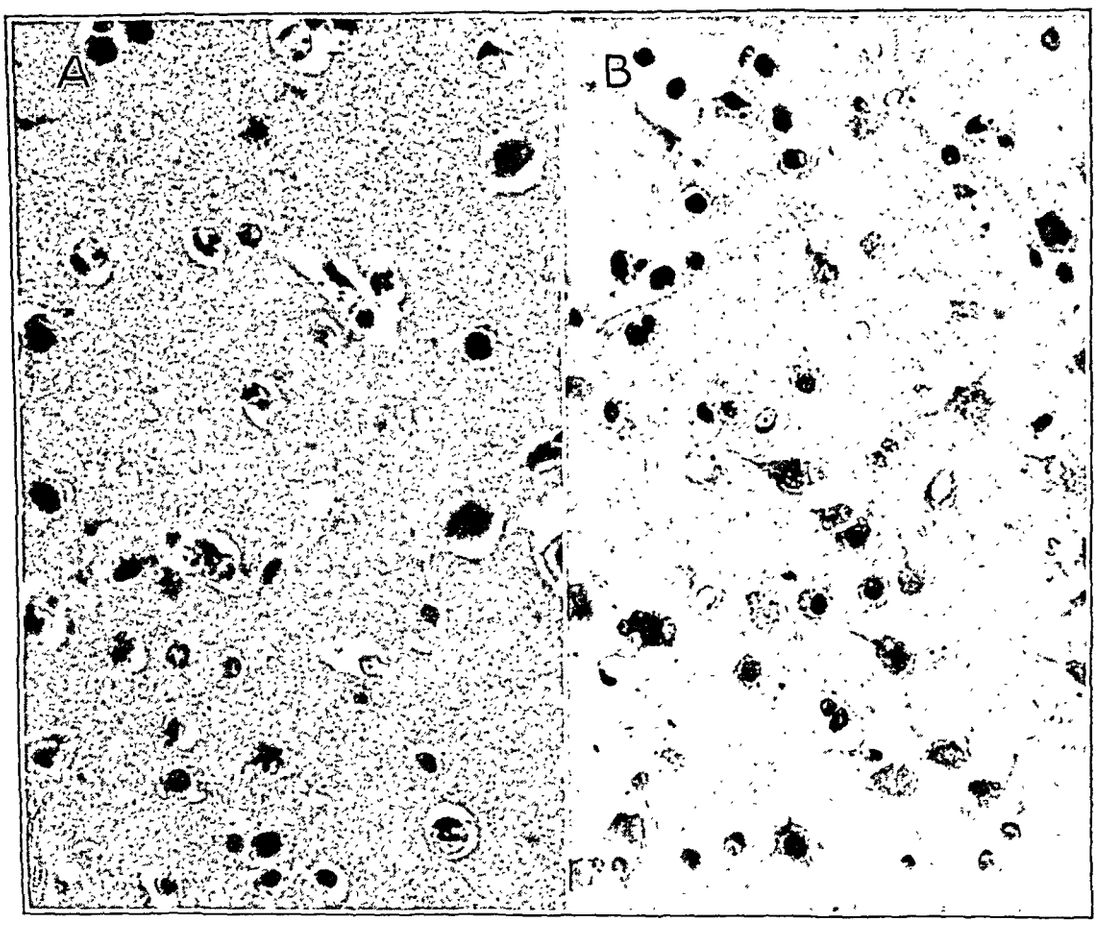

Fig. 2.—*A*, section of the cerebral cortex of the same brain from which sections in figure 1 were taken, showing enlarged perivascular and pericellular spaces resulting from capillary permeability. In our opinion, these changes are too pronounced to be artefacts. Hematoxylin and eosin; × 430. *B*, cells showing various degenerative changes. Thionin stain; × 430.

OBSERVATIONS

Human Brain.—The child, aged 7, was admitted to the hospital with the chief complaint of abdominal pain.[14] Approximately forty hours after admission she was comatose. Malarial parasites were demonstrated in the peripheral blood only four hours preceding death. At this time the total red blood cell count was 1,060,000, the hemoglobin concentration 5 Gm. and the white blood cell count 22,200 per cubic millimeter. Fifteen per cent of these red blood cells were parasitized. Approximately one half of these cells contained from 2 to 4 parasites. The carbon dioxide-combining power was 26 volumes per cent. Autopsy was performed approximately three hours after death.

The convolutions of the brain were slightly swollen. Petechiae were numerous both in the meninges and on the cut section of the cerebrum and cerebellum (fig. 1). These hemorrhages occurred in both the gray and the white matter of the brain; however, they were more numerous in the latter area. The blood vessels in the cerebral cortex were notably congested with parasitized erythrocytes. The endothelial cells lining the vessels were swollen; a few contained granules of pigment and fat, while others were either free in the lumen or partially attached to the vessel wall. The perivascular and pericellular spaces were greatly enlarged, giving to the tissues a cribriform appearance (fig. 2 *A*). Occasionally these spaces were surrounded by a necrotic area.

All the nerve cells in the gray matter of the cerebral cortex appeared to show pathologic changes (fig. 2 *B*). This lesion varied from only a change in the staining reaction to disintegration of the cell. Many nerve cells showed complete exhaustion of the Nissl material. Some of the cells presented sclerotic changes, with pyknotic nuclei, shrunken cytoplasm and tortuous processes. A few cells exhibited pigmentary degeneration, with varying quantities of yellow-brown granules clustered about the nucleus. This pigment usually was more pronounced at the apical poles of the cells. Numerous cells showed acute swelling and vacuolar disintegration. These pathologic changes exhibited neither regional

14. Rigdon, R. H.: A Consideration of the Mechanism of Death in Acute Plasmodium Falciparum Infection: Report of a Case, Am. J. Hyg. **36**:269-275, 1942.

specificity nor uniformity within any given area. The remaining portions of the brain and spinal cord presented similar cell changes. The lesions decreased in severity from the cerebral cortex to the spinal cord. In the latter region altered staining reactions, chromatolysis and hyalinization of the cytoplasm were the changes observed.

The white matter of the brain and spinal cord presented the most spectacular lesions, in contrast to the less conspicuous lesions of the gray substance. In histologic sections of the cerebral hemispheres, the subcortical white matter, the corona radiata and the internal capsule were literally strewn with holes, varying in size from 1.5 to 80 microns in diameter (fig. 3 *B*). The glia and nerve fibers were compact and swollen and were stained more deeply around the margin of these spaces than in the surrounding tissue. Fragments of degenerating fibers might be seen either free or extending across some of the spaces. In this paper we refer to these spaces as "perforate lesions."

These "perforate lesions" were present also in the substantia alba of the cerebellum and in the fiber pathways of the brain stem and the spinal cord. They were fewer, however, than in the cerebral hemisphere. They occurred infrequently in the gray matter.

Another type of lesion observed in the brain was an irregular, oval necrotic area, varying in size from 50 by 100 to 500 by 700 microns (fig. 4 *A*). These foci appeared as light-staining, finely reticulated areas with a dark-staining center. Glial fibers and fragmented demyelinated nerve fibers constituted the lighter-staining tissue, while glia cells, large mononuclear cells, malarial pigment and tissue debris made up the darker center. The number of glia cells varied; many showed amitotic division. Small blood vessels, either intact or fragmented, were present within the necrotic areas. Red blood cells, both parasitized and nonparasitized, were present in varying numbers within these lesions. In some areas the red blood cells were intact; in others they were hemolyzed, while a few showed only fragmented erythrocytes. Large mononuclear cells were also present within these necrotic foci. They had large, open, pale-staining nuclei and prominent nucleoli. Some showed phagocytosed particles within their cytoplasm. These phagocytic cells were sometimes attached to the wall of the fragmented vessels.

Other areas of necrosis, similar to the granulomatous lesions previously described, appeared as irregular, pale-staining patches, varying widely in both size and shape. These gave to the tissue a lacelike appearance. The

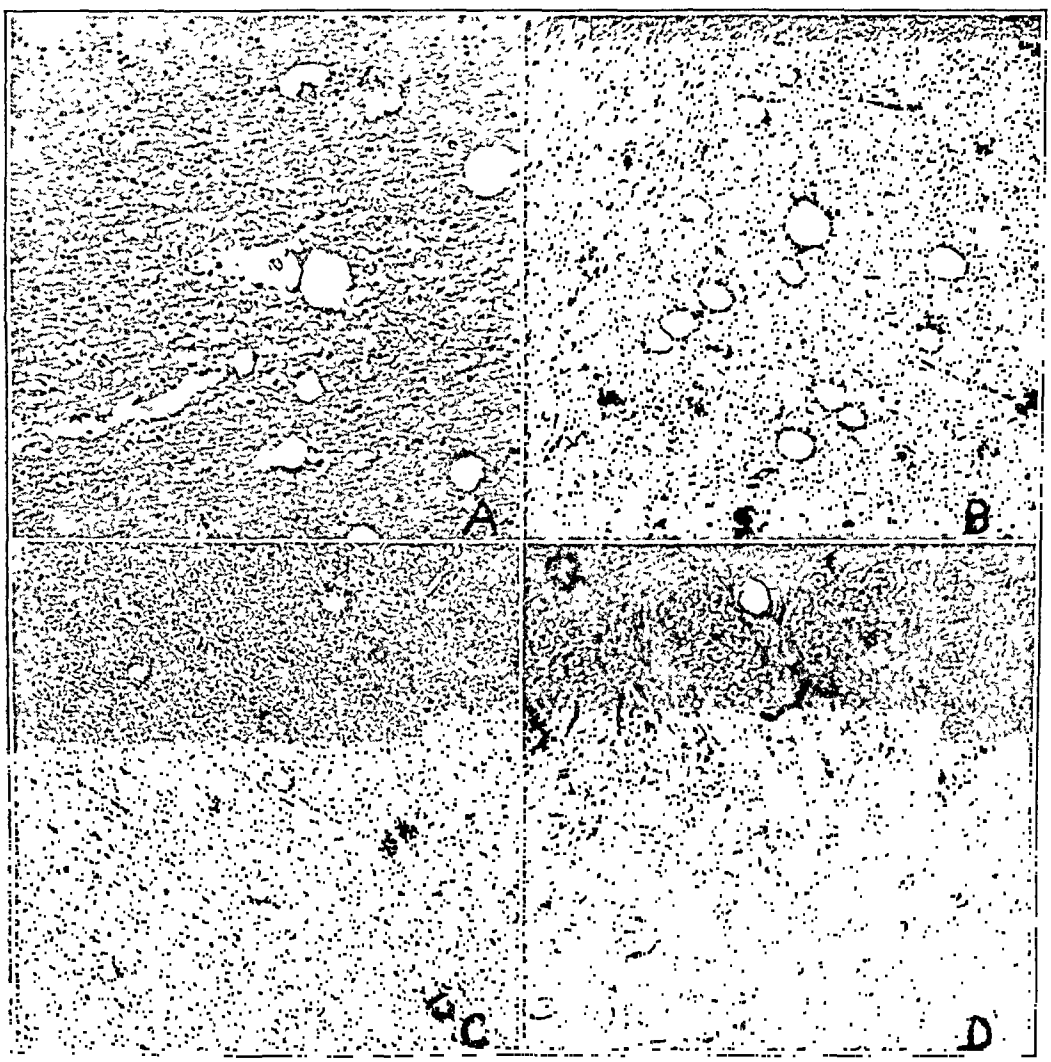

Fig. 3.—Sections from the same brain as that which appears in figures 1 and 2. *A*, areas of necrosis in the corona radiata, with a "lacelike" appearance; *B*, numerous circumscribed spaces referred to in the text as "perforate lesions," varying in size from 1.5 to 80 microns. These lesions gave a cribriform appearance to the internal capsule and the corona radiata of this brain. Similar lesions occurred in the brains of the monkeys, ducks and chicks which were similarly infected. *C*, subcortical white matter of the monkey brain, showing "perforate lesions," preceded by an early degenerative lesion in the myelin, as indicated by variations in staining. *D*, section of the midbrain of the same monkey, showing a picture similar to that in *C*.

number of glia cells was decreased in these areas (fig. 3 *A*).

Focal areas of myelin degeneration 25 to 50 microns in diameter were demonstrated in thick histologic sections. These stained uniformly gray-blue with Weil's technic, light red with thionin and orange-pink with hematoxylin and eosin. The periphery of these lesions stained more deeply than the center (fig. 3 *B*).

Necrotic lesions like those described in the white matter of the cerebrum occurred in the cerebellum, but less frequently. They were more numerous in the molecular layer of the cerebellar cortex than in the substantia alba.

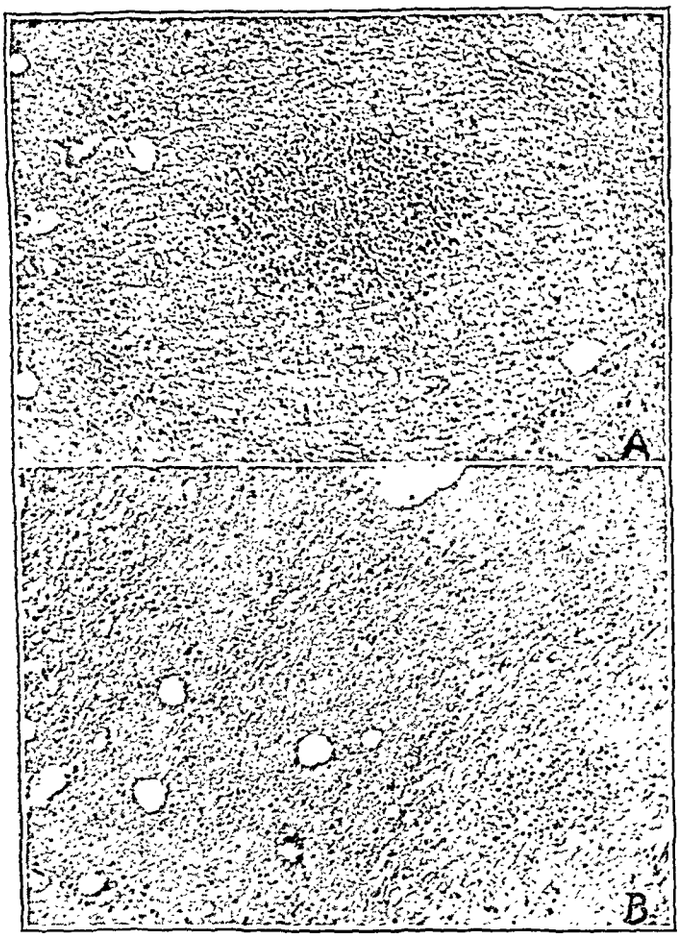

Fig. 4.—Lesions in the white matter of a brain of a child who died of infection with P. falciparum. *A*, "Dürck granulomas," showing extensive glial proliferation; *B*, granulomas, "perforate lesions" and "lacelike" necrosis in the corona radiata. Hematoxylin and eosin; × 100.

The Purkinje cells were greatly reduced in number (fig. 5 *A*). Some of these cells which remained showed acute swelling with chromatolysis; others were sclerotic with tortuous processes, and a few contained granules of yellow-brown pigment about the nucleus. No demonstrable changes were present in the granule, basket and Golgi cells.

Monkey Brain.—The data, as shown in the accompanying table, were obtained from the 3 monkeys used in this study. The brains did not show any significant macroscopic changes. The blood vessels in the brain of monkey 3, which was not perfused, were filled with parasitized cells similar to the vessels in the child's brain. The perivascular and pericellular spaces were enlarged in each of the 3 brains. The cytologic changes were similar in the monkey's brain to those in the child's brain. Focal areas of demyelination were also present. They occurred in both the gray and the white matter throughout the brain and the spinal cord of the 3 monkeys (fig. 3 *C* and *D*). They were more numerous in the cerebrum than in the spinal cord and occurred more frequently in the white than in the gray matter. The "perforate lesion" and the areas of "lacy degeneration" also were present, but were less conspicuous in the monkey brain than in the human brain.

The pathologic changes in the cerebellum were similar to those in the cerebrum. The Purkinje cells were notably depleted (fig. 5 *B*). The remaining Purkinje cells showed chromatolysis and other types of degeneration. The granule, basket and Golgi cells appeared normal.

Duck Brain.—No gross lesions were observed in the brains of the ducks. However, microscopic lesions were present, and basically they were similar to the lesions

Laboratory Data on Monkeys Infected with Plasmodium Knowlesi

Monkey	Experimental Day	Time	Red Blood Cells, Millions	Percentage of Red Cells Parasitized
1	3	9:30 a.m.	3.15	0.4
	4	9:00 a.m.	3.1	4.5
	5	9:00 a.m.	3.15	4.5
	5	2:30 p.m.	....	4.8
	6	9:00 a.m.	1.9	42.6
	6	2:00 p.m.	1.95	46.8
	7	10:00 a.m.	Killed by bleeding	
2	2	.....	....	6.6
	3	.....	....	39.6
	3	.....	Killed by bleeding	
3	2	.....	....	6.3
	3	.....	....	51.7
	3	.....	Killed by bleeding	

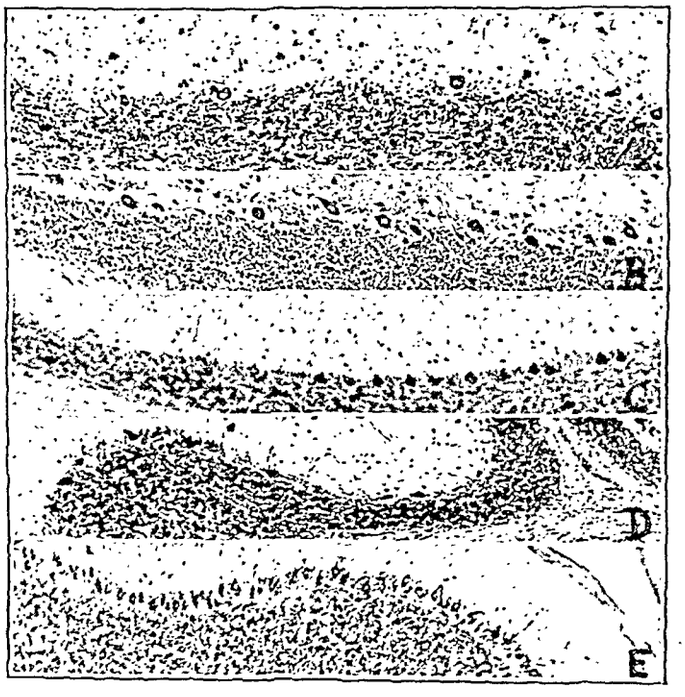

Fig. 5.—Depletion of Purkinje cells of the cerebellum, with varying degrees of degeneration of the remaining cells in a child and in experimental animals infected with malaria. *A* is from the child's brain; *B*, from the monkey brain; *C*, from the duck brain, and *D*, from the chick brain. *E* is a section from the cerebellum of a normal chick, shown for comparison. Thionin stain; × 100.

in both the human and the monkey brain. The changes that occurred in the Purkinje cells in the duck brain during the course of malaria may be considered under the following stages: (1) the normal, or resting stage;

(2) the stage of sclerosis; (3) the stage of edema, showing both early and late phases; (4) the stage of exhaustion and (5) the stage of disintegration.

The normal resting Purkinje cell in the duck brain tended to be pyriform, like Purkinje cells in other animals. The cytoplasm was filled with large, uniformly distributed Nissl flakes. The nucleus, which was oval to spheroid, was centrally placed and filled with acidophilic chromatin material. These granules were distributed over a linin net, dispersed around the inner margin of the nuclear membrane and concentrated about a prominent, centrally placed nucleolus, which consisted of two or three circular bodies. With hematoxylin and eosin the cytoplasm of the normal resting cell stained pale blue and the nuclear structure darker blue. The staining properties were such that the cell was poorly delineated from the surrounding tissue (fig. 6 *A*).

In the second stage the sclerotic cell was shrunken, triangular to spindle shaped and filled with Nissl material The nucleus was pyknotic, eccentric and obscured by the deeply stained cytoplasm The dendritic processes of many of these cells were tortuous (fig. 6 *B*).

The edematous cell in the early phase was approximately twice the size of a normal resting cell. The tigroid substance was depleted except at the periphery, where it appeared in large bodies. The chromatin granules of the nucleus were compressed into a centrally placed, deeply staining mass, surrounded by an edematous area, which stained either clear or cloudy (fig. 6 *C*). Figure 6 *D* showed the late phase of the edematous cell, in which the edema had decreased. The chromatin granules were scattered throughout the nucleus, and the Nissl bodies were piled up about the nucleus and located at the periphery of the cell. The cytoplasm stained a muddy pink with hematoxylin and eosin.

The cell in the exhausted stage appeared as a homogeneous, pale pink–staining mass of protoplasm, with ill defined nucleus and fuzzy outline. The Nissl substance and nuclear chromatin were completely absent. Some of these cells showed vacuolar degeneration and disintegration (fig. 6 *E*).

The number of Purkinje cells in a transverse section of a folium varied in the ducks with malaria as compared with the number in normal ducks. It is of interest to observe that the number of Purkinje cells was least in the ducks which survived the acute stages of the malarial infection and subsequently had neurologic manifestations (fig. 5 *C*). The remaining Purkinje cells showed the various stages of activity and degeneration, as previously described.

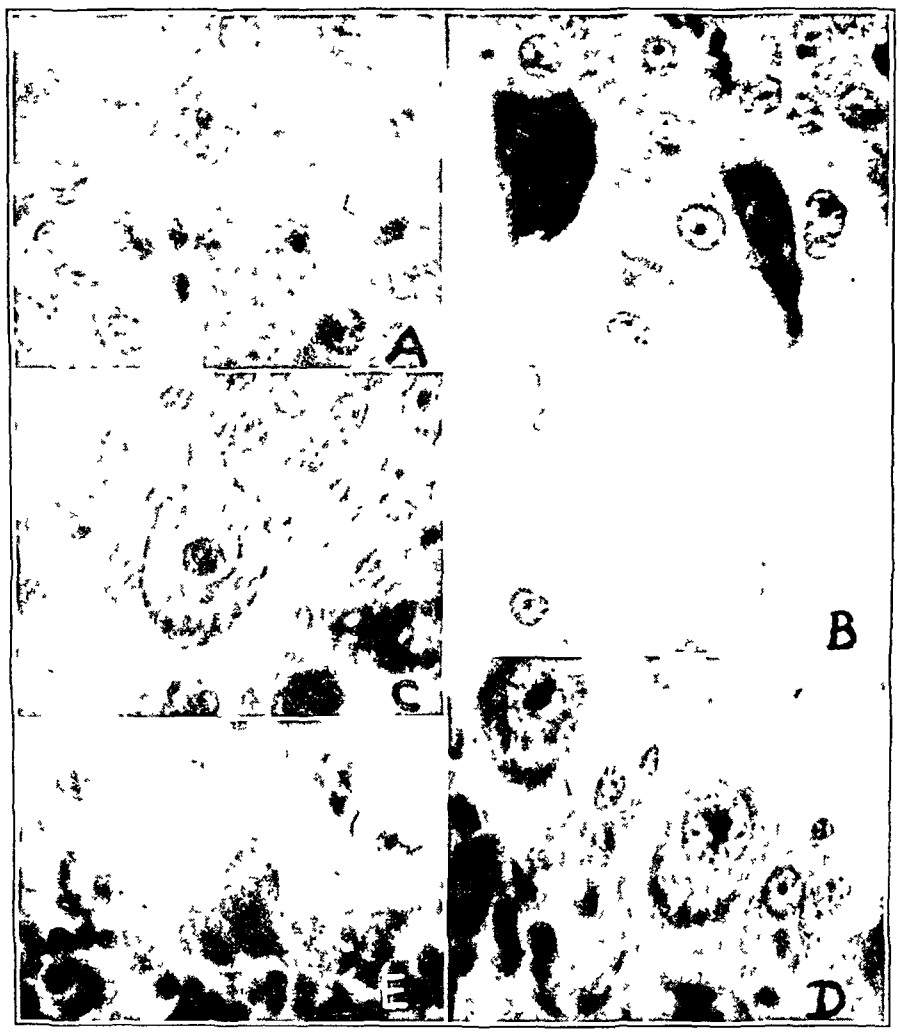

Fig. 6.—Stages of activity and degeneration of Purkinje cells from the cerebellum of a duck infected with malaria. *A*, normal resting cell, *B*, pyknotic cell; *C*, early phase of edematous cell; *D*, late stage of edematous cell, and *E*, exhausted cell. Hematoxylin and eosin; × 910.

The cells in the nuclei of the cerebellum showed pathologic changes similar to those in the Purkinje cells. Acute swelling and vacuolar degeneration occurred in these nuclear cells in the moribund bird (fig. 7).

Chick Brain.—The pathologic changes in the cerebellum of the chick were similar to those in the duck. The depletion of the Purkinje cells in a chick with

malaria is shown in figure 5 *D*. This may be compared with the condition in the brain of the normal chick (fig. 5 *E*).

COMMENT

The lesions which we have described in the brain and spinal cord in association with malaria were fundamentally and basically the same in the child, monkey, duck and chick.

Edema was a constant feature. It could be detected even grossly. In histologic section it appeared as a notable enlargement of the perivascular and pericellular spaces. We are cognizant of the fact that a similar process may occur as a technical artefact. However, we consider it too pronounced for an artefact and believe that it is the earliest lesion associated with malaria.

Fig. 7.—Cells in the cerebellar nuclei of a duck with a severe malarial infection, showing vacuolar degeneration. Thionin stain; × 430.

The nerve cells in the cerebral cortex of the child were more severely damaged than those in the monkey. These cytologic changes were less pronounced in the more caudal regions of the brain. This variation in the human and in the monkey brain may have been influenced by the degree of parasitemia, the length of the infection and the susceptibility of the brain to injury.

The Purkinje cells of the cerebellum were depleted in the human, monkey, duck and chick brains. The progressive changes which precede this depletion were followed in the duck and chick brains. We recognize that all these cell changes were not pathologic. The earlier ones may represent normal physiologic activity of the cell in response to some stimulus in malaria. The later changes were irreversible and led to death of the cell. These changes in the Purkinje cells are not specific for malaria. Similar ones have been described in cases of fatigue and exhaustion,[15] shock,[16] anemia [17] and many other conditions.[18]

In the literature which we have reviewed three specific lesions have been described, namely petechiae,[1] malarial nodules [4] and the Dürck granulomas.[6] Each of these lesions has been observed in our studies; in addition, we have noted other degenerative changes in the myelin, the earliest manifestation of which was a variation in staining. Later the myelin might be partially or completely removed, leaving either perforations or focal areas of demyelination with a "lacelike" appearance. Petechiae were present in the child's brain; they occurred only in the focal areas that we have referred to as granulomas. It is of interest to observe that red blood cells were not present in all the areas of necrosis. This observation suggests that the hemorrhages were secondary to the necroses. Why should red blood cells occur in one area of necrosis and not in another?

It appears more reasonable that the answer lies in the vascular supply about the necrotic area. In the focal areas of necrosis the circulation is maintained. In contrast, in the diffuse, "lacelike" areas of degeneration the blood flow has ceased. In such areas, purely by chance, a greater number of parasitized red blood cells accumulate within the lumens, thereby obstructing the circulation. Inasmuch as the blood flow has ceased, it is obvious that hemorrhage cannot occur. This process has been interpreted as thrombosis. In our opinion it is only the end result of stasis.

It is easy to understand how one would conclude from seeing histologic sections of the brain in cases of infection with P. falciparum that the

15. Hodge, C. F.: A Microscopical Study of Changes Due to Functional Activity in Nerve Cells, J. Morphol. **7**:95-168, 1892. Dolley, D. H.: The Neurocytological Reaction in Muscular Exertion: I. Preliminary Communication; the Sequence of the Immediate Changes in the Purkinje Cells, Am. J. Physiol. **25**:151-171, 1909-1910.

16. Dolley, D. H., and Crile, G. W.: The Pathological Cytology of Surgical Shock: I. Preliminary Communication; the Alterations Occurring in the Purkinje Cells of the Dog's Cerebellum, J. M. Research **20**:275-295, 1909.

17. Dolley, D. H.: The Morphological Changes in Nerve Cells Resulting from Overwork in Relation with Experimental Anemia and Shock, J. M. Research **21**:95-113, 1909.

18. (*a*) Courville, C. B.: Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif., Pacific Press Pub. Assoc., 1939, p. 150. (*b*) Hartman, F. W.: Some Etiological Factors and Lesions in Cerebral Anoxia, Am. J. Clin. Path. **8**:629-648, 1938.

capillaries are occluded either by thrombi or by emboli. However, as far as we have been able to determine from a review of the literature, no one has observed the progressive development of a thrombus on the walls of the vessels in the brain in a case of malaria. Furthermore, in our study we have not observed such a process. The presence of a sufficient number of parasitized red blood cells to fill the lumen of capillaries should not be interpreted necessarily as an embolus. Masses of parasitized red blood cells have been demonstrated only infrequently in the peripheral blood of patients with malaria.[19] If emboli are characteristic of malaria, it would seem that the evidence from the numerous studies already made on this disease should be conclusive. The demonstration of a variety of pathologic changes unassociated with thrombi and emboli in the brains of man and experimental animals, such as the monkey, duck and chick, as shown in this paper, suggests that another mechanism may account for the pathogenesis of the hemorrhages present in the brain in cases of acute malarial infection.

The focal areas of necrosis observed in the brain of the child, monkey, duck and chick were similar to the lesions described by Dürck [6] and Margulis.[5] In the lesions described by Dürck, and now known as "Dürck granulomas" a large number of glia cells accompany the necrosis. It is suggested that a period must elapse to permit this glial reaction to occur.

The pathologic lesions in the brain of both man and the experimental animals infected with malaria are identical with changes in a series of animals which Hartman [18b] concluded to be the result of anoxia. It has been suggested by one of us (R. H. R.) that the pathologic lesions in the viscera of man, monkey and duck may be influenced in their development by anoxia.[20]

The patient whose brain was used for this study had only approximately 1,500,000 red blood cells at the time of death. In monkeys, likewise, rapid anemia developed. The red blood cells in the ducks frequently decreased within forty-eight hours from 2,200,000 to 600,000. This rapidly progressing anemia apparently was responsible for the anoxia. It is only reasonable to believe that because the malarial parasites utilize hemoglobin, parasitized red blood cells do not carry the same quantity of oxygen as nonparasitized cells. The myocardium may become anoxic and the circulation slowed, thus producing a stagnant type of anoxia. Anoxia therefore appears to be the basis for the development of the cerebral lesions in malaria.

19. Schüffner, W. A. P., and Esseveld, H.: Causes of Malignancy of Tropical Malaria, Geneesk. tijdschr. v. Nederl.-Indië **76**:3038-3045, 1936; abstracted, Trop. Dis. Bull. **34**:383, 1937. Cropper, J.: Phenomenal Abundance of Parasites in a Fatal Case of Pernicious Malaria, Lancet **2**:16-17, 1908.

20. Rigdon, R. H., and Stratman-Thomas, W. K.: A Study of the Pathological Lesions in P. Knowlesi Infection in M. Rhesus Monkeys, Am. J. Trop. Med. **22**:329-339, 1942. Rigdon, R. H.: A Pathological Study of the Acute Lesions Produced by P. Lophurae in Young White Pekin Ducks, ibid. **24**:371-377, 1944; footnote 14.

PATHOGENESIS OF LESIONS IN THE BRAIN ACCOMPANYING MALARIA

Our pathologic studies suggest that an increased permeability occurs in the capillaries of the brain in cases of severe malaria, as indicated by the enlargement of the perivascular and pericellular spaces (fig. 2*A*). This increase in permeability is the result of anoxia. Accompanying this increased permeability of the capillaries is anoxia of the adjacent parenchymatous tissue, as indicated by the focal changes in the myelin. Such foci are apparent from the variation in staining (fig. 3). As the process of anoxia continues the myelin in these focal areas degenerates. The permeability of the capillary walls may be sufficiently impaired to permit the escape of parasitized and nonparasitized red blood cells. Such cells may partially or completely fill the foci of myelin degeneration and may extend into the surrounding tissue, producing the classic petechiae, as observed with the severe types of malaria. With the lapse of time glial and mononuclear cells may proliferate in these areas of necrosis.

The cytologic changes as observed in the nerve cells of the cerebral cortex and the Purkinje cells of the cerebellum in this study are, in our opinion, also the result of anoxia.

Accompanying the development of the neurologic lesions are severe pathologic changes in the other viscera of the body. The myocardium and the peripheral circulation are severely affected, and the rate of circulation decreases throughout the brain. This slowing of the circulation increases the cerebral anoxia. The parasitized red cells apparently tend to localize along the wall of the capillaries and may interfere with the function of the endothelial cells. All the metabolic processes within the brain, therefore, may be progressively impaired until death results.

SUMMARY

The pathologic lesions occurring in the brain of a child who died in the acute stage of infection with P. falciparum and in brains of the monkey, duck and chick infected with malaria were similar. The gray and the white matter of the entire brain and spinal cord were sometimes involved; however, the cerebral hemispheres and the cerebellum showed the most extensive injury. These neurologic lesions may result from anoxia.

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CHARACTERISTIC ROENTGENOGRAPHIC CHANGES ASSOCIATED WITH TUBEROUS SCLEROSIS

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Knowledge of the presence of characteristic roentgenographic changes in the skull of patients with tuberous sclerosis has been a fairly recent addition to the diagnostic criteria of this disease entity. In 1924 Marcus [1] described the roentgenogram in a case of tuberous sclerosis, as follows:

> In several places within the cranium were calcified areas the size of a bean or pea, with layers of "chalk shale." Most such areas were located in the middle fossa on the left side, but several were visible in the parietal regions.

Dalsgaard-Nielsen stated that Marcus' case is the first published instance of tuberous sclerosis with roentgenographically discovered calcification in the cerebrum. In 1935 Dalsgaard-Nielsen [2] published the following description of the calcifications noted in roentgenograms of the skull of a 14 year old boy with convulsive seizures and adenoma sebaceum.

> The shape of the cranium is normal. The sella turcica is small but otherwise normal. Scattered throughout the roentgenogram of the skull are numerous osseous shadows. They are irregular in form and size and in great part slightly "watery," but their density is variable. No destruction of bone is seen. Many of these shadows are situated in the calvaria and may be assumed to be hyperostotic changes. Not a few are doubtless located in the cerebrum itself and appear there as spreading, small and irregular calcifications in the left hemisphere. One calcification lying at about the middle of the left frontal lobe is the size of an orange. The rest of the skeletal system shows no roentgenographic changes.

Later, Gottlieb and Lavine [3] described analogous roentgenographic changes in another case of tuberous sclerosis. Yakovlev and Corwin [4] reported the roentgenographic demonstration of multiple discrete areas of calcification throughout the brain. Heublein, Pendergrass and Widman [5] described the calcifications seen in their cases as being within the brain substance, and in 1 instance possibly within the calvaria. Pancoast, Pendergrass and Schaeffer [6] stated:

> . . . not infrequently the bones of the extremities and occasionally of the calvaria show changes which include periosteal deposits and cystic or "punched out" areas in the spongiosa.

In a recent publication, Ross and I [7] stated that the chief roentgenographic finding in tuberous sclerosis, that of patchy zones of increased density in the skull, is located in the calvaria. These zones occurred in half our cases. We have been unable to find any description of the structural changes which occasion this appearance.

One of the patients in our previous study known to be hemophilic, presented the characteristic roentgenographic features of tuberous sclerosis. Most of the diagnostic studies performed on the other patients in that series were omitted with this patient because of the difficulty in control of bleeding following such simple procedures as venipuncture and the withdrawal of blood from the finger tip for routine studies of the blood. The patient has since died, and autopsy was performed. We believe that the following presentation is the first detailed description of the location and nature of the structural changes giving rise to the roentgenographic lesions which he presented.

REPORT OF CASES

CASE 1.—*History.*—L. B., a white boy, was admitted to the Caro (Mich.) State Hospital for Epileptics on July 25, 1942; at that time he was 10 years of age. Both the paternal and the maternal branch of the family showed several neuropathic deviations. The mother had

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1. Marcus, H., cited by Dalsgaard-Nielsen.[2]

2. Dalsgaard-Nielsen, T.: Tuberøs sclerose med sjaeldent røntgenfund, Nord med. tidskr. **10**:1541 (Sept. 28) 1935.

3. Gottlieb, A. S., and Lavine, G. R.: Tuberous Sclerosis with Unusual Lesions of the Bones, Arch. Neurol. & Psychiat. **33**:379 (Feb.) 1935.

4. Yakovlev, P. I., and Corwin, W.: A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple "Brain Stones"), Arch. Neurol. & Psychiat. **42**:1030 (Dec.) 1939.

5. Heublein, G. W.; Pendergrass, E. P., and Widman, B. P.: Roentgenographic Findings in the Neurocutaneous Syndromes, Radiology **35**:701 (Dec.) 1940.

6. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 663.

7. Ross, A. T., and Dickerson, W. W.: Tuberous Sclerosis, Arch. Neurol. & Psychiat. **50**:233 (Sept.) 1943.

fainting spells and was considered a religious fanatic. The father was described as mentally deficient. Our patient was the oldest of 5 children, the others apparently being normal. The birth and developmental histories were not unusual. At the age of 6 months he cut his mouth and bled for two weeks. He began to have convulsions a month later, and the attacks continued until his death. He was greatly retarded in walking and never learned to talk.

He was admitted to the University Hospital, Ann Arbor, Mich., when 3 years of age because of convulsions. There he was resistive to every examination. The general physical examination revealed nothing significant except for a scattered papular eruption over the body. The neurologic examination was unsatisfactory, and the reflexes were normal as far as could be determined. Ophthalmologic examination revealed nothing abnormal. All laboratory examinations, including studies of the spinal fluid, yielded normal results. Roentgenograms of the skull were considered to be within normal limits. A pneumoencephalogram showed moderate dilatation of the ventricles, slightly greater on the left side. The subarachnoid channels over the right cortex were incompletely drained There was no gross displacement of the ventricular system. During his stay in the hospital he was given three small transfusions of blood because of long-continued hemorrhage from a laceration of the tongue which he received during a seizure. He was discharged without medication; the final diagnosis was grand mal epilepsy.

When 10 years of age he was admitted to a nursing home with second and third degree burns, which he had received in a seizure. They covered approximately one third of the body. In addition to his untidiness and restiveness, many hemorrhages from the granulating surfaces of the wounds added to the difficulties of his care. Four months later he was transferred to the Caro State Hospital.

Examination.—The patient was pale and underdeveloped, obviously at the idiot level of intelligence. He made no attempts to speak and drooled continually. There were many incompletely healed burns over the lower extremities and a slight contracture of the right knee. He was able to walk. Sebaceous adenomas were present in typical butterfly distribution over the nose, cheeks and nasolabial folds. There were three café au lait spots on the face: (1) one measuring 5 by 1.5 cm., extending from the brow to the hair line on the right side of the forehead; (2) one, measuring 1 by 0.75 cm., situated immediately above the right angle of the mouth, and (3) a similar spot on the left cheek, at the midpoint of the horizontal ramus of the mandible. The rest of the general physical examination revealed nothing significant. The neurologic examination showed only a Babinski sign on the left side. The ocular fundi could not be visualized. The kidneys were not palpable.

Routine laboratory examinations revealed only moderate secondary anemia. The Kahn reaction of the blood serum was negative. No other laboratory examination was attempted. Roentgenograms of the skull (fig. 1 *A*) demonstrated many islands of increased density throughout the cranium. In stereoscopic views these appeared to be within the calvaria. There was also a small area of increased density, of irregular outline, in the posterior fossa. Roentgenograms of the chest showed nothing abnormal.

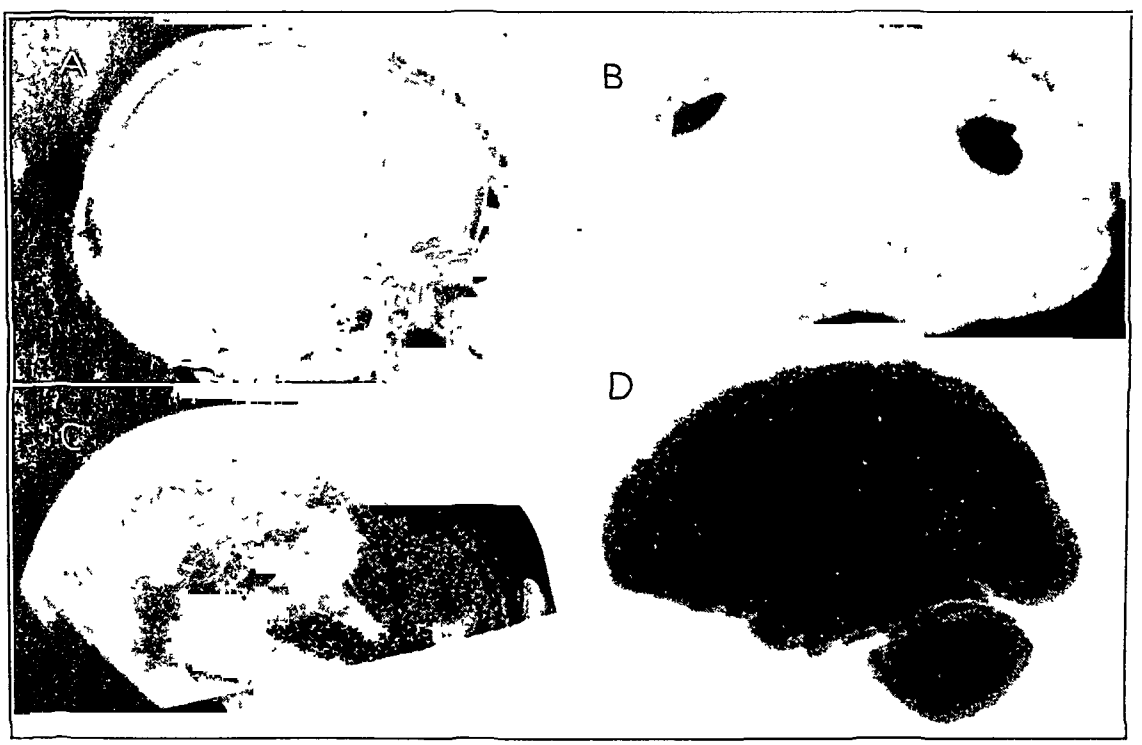

Fig. 1 (case 1).—*A*, roentgenogram of the skull in the lateral projection, demonstrating the islands of increased density which are the chief roentgenographic sign in cases of tuberous sclerosis. An indistinct area of increased density is also seen in the posterior fossa. *B*, photograph of the calvaria obtained by transillumination, demonstrating the increased translucency of the involved areas. The sites of removal of the buttons of bone for histologic examination were sealed with black photographic paper. *C*, roentgenogram of the calvaria, demonstrating that the islands of increased density are situated in the calvaria. *D*, roentgenogram of the brain. The islands of increased density seen in roentgenograms of the skull are not visible. The area of calcification seen in the posterior fossa in *A* appears here in the cerebellum. If the dense areas of the roentgenograms of the skull were due to calcification in or around the cortical nodules, they should also be visible here.

Course in the Hospital.—The patient continued to experience many convulsive attacks. He received several injuries during seizures; the slightest break in the skin or mucous membranes was always the site of a brisk hemorrhage. Injections of a solution of brain extract and a preparation of vitamin K were seldom successful in controlling the bleeding; he received three transfusions. He died suddenly, apparently in a seizure.

Autopsy.—General Observations: The skin and subcutaneous tissues of the face, neck, trunk and extremities showed pitting edema. Pigmented areas and sebaceous adenomas occurred on the face, as well as many healed scars on both lower extremities. The usual incision in the scalp bisected a plaque measuring 4 cm. in diameter and 0.5 cm. in thickness, of orange color and granular appearance, situated immediately to the right of the midline. Here and there in the calvaria could be seen areas, roughly circular in outline and varying from 0.3 to 1.5 cm. in diameter, of a deeper yellow than the surrounding bone; however, there was no change in the consistency of the bone. When the calvaria was removed, these areas were more translucent to light than the surrounding bone (fig. 1 *B*). On the inner surface, each of these areas was more grayish and was slightly indented below the level of the surrounding bone. The dura was approximately twice the normal thickness.

The abdominal cavity and the pericardial sac contained increased amounts of clear, straw-colored fluid. The spleen was large and boggy, weighing 260 Gm. The surfaces of both kidneys were studded with many small yellow tumors, varying from 0.3 to 1.5 cm. in diameter. At the upper pole of the right kidney there was a larger tumor mass, approximately the size of a silver dollar and 1 cm. in thickness. Two small subcapsular cysts were seen in the left kidney; within the substance of the left kidney was a tumor nodule, about 1 cm. in diameter.

Histologic Study (Dr. H. E. Cope, Michigan Department of Health): The lesion of the scalp was an old degenerating hematoma. A pigmented area from the right cheek contained numerous sebaceous glands, about which there was an inflammatory reaction of moderate intensity. The lungs exhibited moderate edema. Some sections of the liver contained many focal areas of infiltration with round cells and a moderate number of polymorphonuclear cells. This focal reaction was not periductal. The appearance of the spleen was not unusual. The renal tumors were made up of cells of varying size and shape, some of which resembled striated muscle. Other cells were not differentiated, and a few large multinucleated cells were seen. In the main, the tumors were fairly well differentiated and well encapsulated; they contained many thick-walled blood vessels.

The pathoanatomic diagnosis was rhabdomyomas of the kidneys, adenoma sebaceum, degenerating hematoma of the scalp, focal subacute hepatitis and pulmonary edema.

A roentgenogram of the calvarium (fig. 1 *C*) showed that the large areas of increased density seen in the roentgenograms of the skull were located within the calvaria. A roentgenogram of the brain after fixation (fig. 1 *D*) demonstrated that the islands of increased density which had been seen in roentgenograms taken during life and in roentgenograms of the calvaria were not visible. The calcified area seen in the posterior fossa in the roentgenograms of the skull was in the cerebellum.

Two buttons of bone were removed, each 2.5 cm. in diameter and each containing one of the areas in question, as confirmed by subsequent roentgenograms. These were examined by Dr. Carl V. Weller, of the department of pathology, University Hospital, Ann Arbor, Mich. His report follows.

Fig. 2 (case 1).—Low power photomicrograph of a section from one of the islands of bone removed from the calvaria. Hyperostosis of the inner table and of the trabeculae of the diploic spaces is demonstrated. The normal bone marrow has been replaced by fat.

"The dense patches in this bone were areas of osteosclerosis, in which the marrow spaces of the cancellous bone of the diploic area had largely disappeared, owing to a concentric development of bone on the previous trabeculae (fig. 2). There was no evidence of neoplasm. It was evident that in the region of osteosclerosis the marrow was fatty instead of cellular. I am not prepared to make any suggestion as to why one region, rather than another, was selected for this change."

Brain: The brain was examined by Dr. Nathan Malamud, of the laboratory of neuropathology at the Neuropsychiatric Institute, Ann Arbor, Mich. His report follows.

"Gross examination: The brain was rather small. The leptomeninges were delicate, and on their removal the convolutional pattern of the brain was observed to be interrupted by pearly white, slightly raised, nodular patches of varying size, which were cartilaginous and hard, with roughened surface and occasionally umbilicated centers. These patches were scattered indiscriminately over the entire cerebrum but were most numerous in the frontal lobes. On the right side, five nodules were noted in the superior frontal gyrus; one each in the orbital, middle and inferior frontal gyri;

one in the postcentral gyrus parasagittally, and two in the angular and the lateral occipital gyrus respectively. On the left side, there were five nodules in the superior frontal gyrus, two in the middle frontal gyrus, one in the precentral gyrus, one in the superior parietal gyrus, one in the supramarginal gyrus, two large nodules in the middle temporal gyrus and one in the inferior temporal gyrus. No definite nodules could be made out on the inferior and median surfaces of the hemispheres. On section, the nodules were distinguished by their white surface and grayish centers, with poor demarcation between the cortex and the white matter. There was moderate hydrocephalus, and the ventricles were studded along their surfaces with numerous tumor nodules, resembling candle gutterings. The brain stem and the cerebellum were not grossly altered.

"Histologic examination: Tuberous nodules in the cortex showed characteristic delamination, decrease in the number of neurons, extensive gliosis and monster nerve and glial elements spreading into the white matter. Examination of the subependymal tumors showed extremely fibrous spongioblastomas, with considerable calcification. There were a few greatly calcified cerebellar nodules.

"The diagnosis was tuberous sclerosis."

An additional case (mentioned as case 2 in the previous paper [7]) likewise demonstrated that the areas of increased density in question are situated in the calvaria. A brief summary follows.

CASE 2.—A woman aged 29, an Austrian Jew, had a feebleminded grandfather and two feebleminded sisters, neither of whom had convulsions or presented facial lesions. She had had a great number of grand and petit mal seizures since the age of 11 years. She had never talked, fed or dressed herself and was untidy. Her mental development was that of an idiot. She was physically underdeveloped and resistive; she usually sat cross-legged and made stereotyped rocking movements. Sebaceous adenomas were present over the face. She walked on everted feet. Both kidneys were palpable, the left seeming to be of normal size and the right slightly enlarged. The external rectus muscles were weak. Far out on the temporal portion of each ocular fundus were deposits of pigment, suggesting old chorioretinitis. On the medial margin of the patch in the right eye was a small, round, yellowish lesion with a nodular appearance. Neurologic examination revealed nothing abnormal.

Laboratory Data.—A complete blood count, a Kahn test of the blood and examination of the spinal fluid gave normal results. The urine contained a trace of albumin and a few granular casts. A biopsy specimen

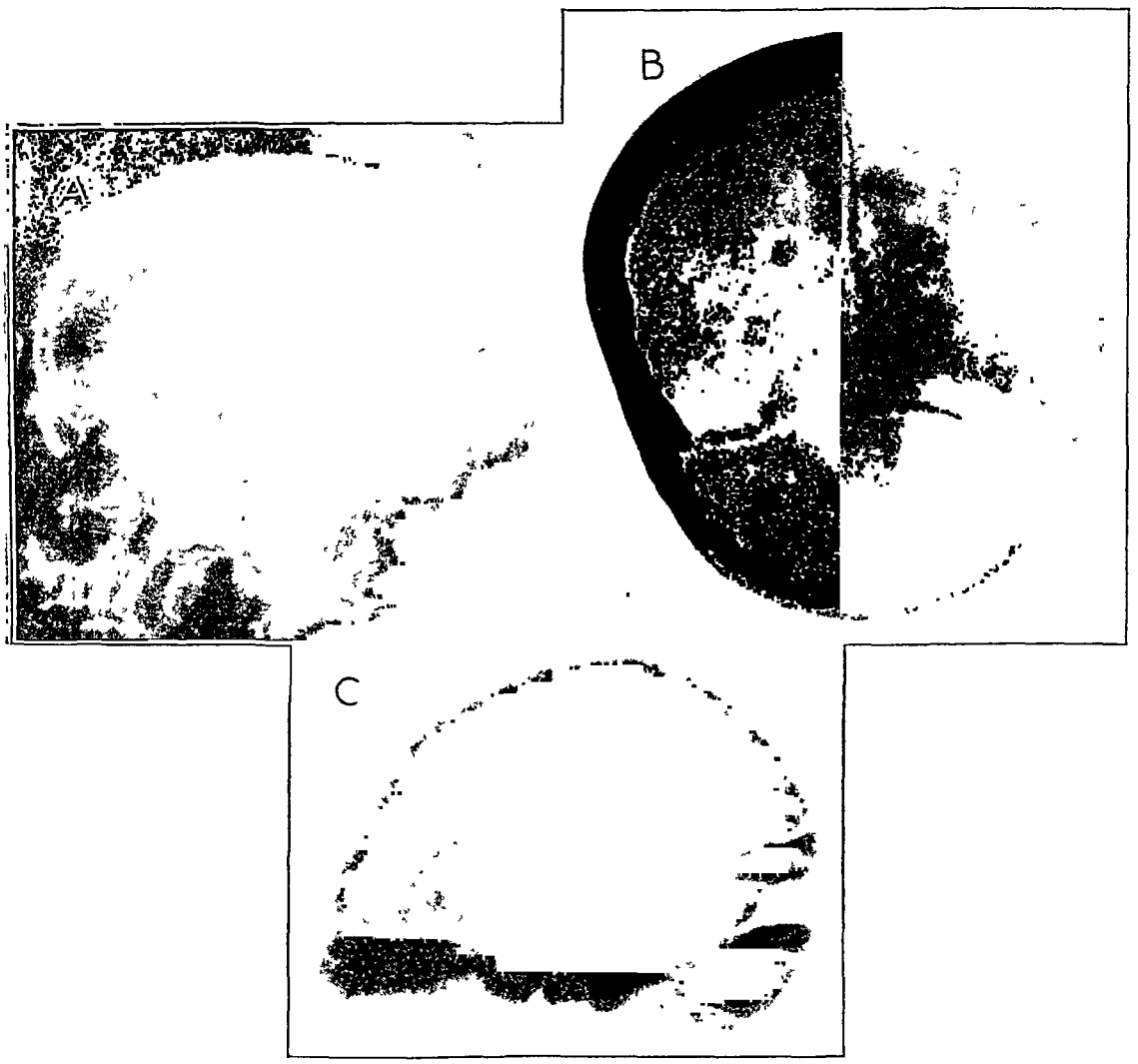

Fig. 3 (case 2).—*A*, roentgenogram of the skull in lateral projection, demonstrating the characteristic islands of increased density. *B*, roentgenogram of the calvaria (vertical projection). The islands of increased density seen in *A* are here present. *C*, roentgenogram of the brain after fixation. The islands of increased density are not visible.

taken from one of the facial lesions was diagnosed as "adenoma sebaceum."

Roentgenographic Findings.—Roentgenograms of the skull (fig. 3 *A*) showed patchy zones of increased density in the cranial vault, but there was no evidence of intracranial calcification. The flat bones of the skull were relatively thick. There appeared to be diminution in volume of the cranial cavity, similar to that seen in microcephaly. Pneumoencephalograms showed a generalized atrophy or hypoplasia of the brain.

Course in the Hospital.—Seizures recurred at irregular intervals. In the course of a year both kidneys, particularly the right, became considerably enlarged. The patient died of bronchopneumonia following a series of seizures.

Autopsy.—Examination of the brain post mortem confirmed the clinical diagnosis of tuberous sclerosis with subependymal tumors in the ventricles. Both kidneys were considerably enlarged; histologic examination gave the brain itself. Gottlieb and Lavine reported thickening of the tables of the skull and a peculiar mottling, with indistinct islands of increased density alternating with areas of rarefaction. Yakovlev and Corwin attributed these areas of increased calcification to degenerative changes at the periphery of the tuberous nodules in the cerebral cortex.

My present study demonstrates that Dalsgaard-Nielsen's first statement was essentially correct. Figure 2 shows that the increased radiopacity was due chiefly to hyperostosis of the inner table of the calvaria, although the hyperostosis was not limited to that structure alone. The material obtained at autopsy in all 3 cases reported in the previous paper, as well as in the

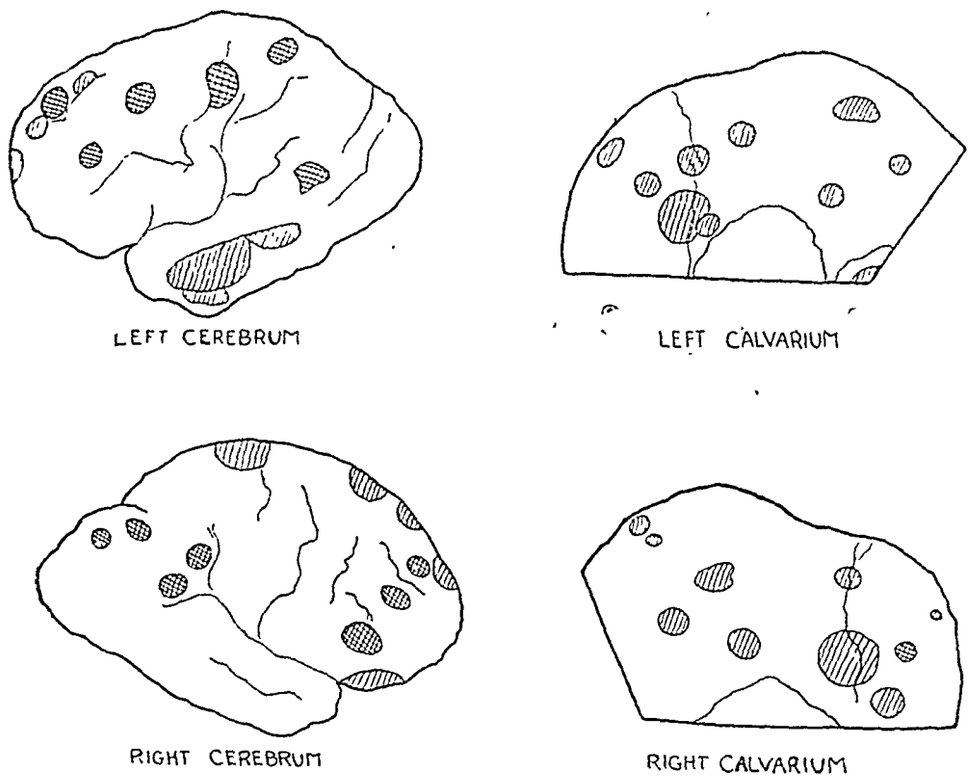

Fig. 4.—Line drawings showing the location of the cortical nodules in the cerebrum and of the involved areas in the calvaria. The cortical nodules indicated by cross hatching lay immediately beneath islands in the calvaria.

a diagnosis of rhabdomyomas undergoing extensive fatty degeneration. A single roentgenogram of the calvaria taken in the vertical projection (fig. 3 *B*) confirmed the impression that there were patchy zones of increased density in the cranial vault. A single lateral roentgenogram (fig. 3 *C*) of the brain after fixation showed no demonstrable calcification.

COMMENT

In previous publications, widely varying opinions have been expressed as to the nature and location of the characteristic calcifications seen in roentgenograms of the skulls of patients with tuberous sclerosis. Dalsgaard-Nielsen stated that some of them were purely hyperostotic formations of the internal lamina; he expressed the belief that others were apparently located within

present case, showed small calcareous deposits throughout the subependymal nodules and basal ganglia; they were present in 80 per cent of the roentgenograms in the entire series of cases. Other investigators, as well as my colleagues and I, have mentioned that these deposits might be confused with other calcifications in the glomus of the choroid plexuses, basal ganglia and pineal body. They were not seen in the present case, either in roentgenograms obtained during life or in the roentgenograms of the brain after fixation. However, these deposits, when visible in roentgenograms, in no way resemble the larger areas in question and are not apt to be confused with them.

I am unable to demonstrate any rarefaction of the bone surrounding the islands of increased density, as suggested by Gottlieb and Lavine. If such areas were present, one would expect them to be less translucent to light than the surrounding bone; figure 1 *B* shows the reverse to be true. It appears that the increased translucency is due to two factors: (1) a diminution in the thickness of the bone in these areas and (2) replacement of normal bone marrow by fat in the involved areas. The latter also accounts for their gross appearance of being slightly more yellow than the surrounding bone.

Dalsgaard-Nielsen stated his belief that most areas of calcification were present within the neoformations of the cortex but that the hyperostoses in the internal lamina were independent processes; admittedly, they might arise from the local irritant action of adjacent tumors. I have recorded as closely as possible by line drawing (fig. 4) the location both of the islands of increased density in the calvaria and of the cortical nodules in the cerebrum. In a majority of instances the bony islands overlay cortical tumors. It is likely that if a more accurate record had been made at autopsy this relation would be more impressively demonstrated.

The "multiple brain stones" of Yakovlev and Corwin, as demonstrated in the roentgenograms shown in their article, cannot be accounted for by the calcareous deposits shown in their illustration of calcification, either in a subependymal nodule or in the white matter underlying a tuberosclerotic nodule in the cortex. I am unable to find that either of their photomicrographs was of autopsy material derived from the cases in which roentgenograms are shown. Calcification, to produce the typical roentgenographic appearance, would have to occur on the surface of the cortical nodules. My colleagues and I have not seen calcification within the "potato patches" or adjacent white matter in any of our 5 cases of tuberous sclerosis in which autopsy has been performed although 2 patients were well past the age of puberty; characteristic roentgenographic changes were present in 3 cases.

In our previous paper, Ross and I reviewed the cases of 12 patients from the Caro State Hospital, together with that of a new patient since admitted, whose roentgenograms of the skull showed the typical islands of increased bone density. No means were available by which the age at which the islands became visible in roentgenograms could be determined. However, the patients at the time the islands were discovered were all beyond the age of 10 years, the patient in the present case being the youngest. Of the 10 patients from the Caro State Hospital, together with 1 patient since admitted, in whose roentgenograms of the skull the islands were not seen, 7 were below the age of 8 years; the remaining 4 patients were 12, 17, 18 and 36 years of age respectively at the time of examination. It is likely, as suggested by Yakovlev and Corwin, that the appearance of these islands of increased density is in some way related to the changes of puberty. None were seen before that age, and they were present in 13 (76 per cent) of the 17 patients examined who were at the age of puberty or older. We have no comment to offer at this time with regard to the significance of this observation.

SUMMARY

The chief roentgenographic sign of tuberous sclerosis, that of patchy zones of increased density in the skull, is located in the calvaria. The roentgenographic appearance of these islands is due to structural changes in the bone, namely, hyperostosis not only of the inner table but also of the trabeculae of the diploic spaces. In addition to the hyperostotic changes, the calvaria is diminished in thickness, and the normal marrow is replaced by fat, rendering the involved areas more translucent to light and visible to the eye. There is no rarefaction of the surrounding bone. Many, if not all, of these islands overlie tuberous nodules in the cerebral cortex. The appearance of the islands of increased density seems to be in some way related to the changes of puberty; the reason for their appearance at this time remains unknown.

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HEMIFACIAL SPASM

REVIEW OF ONE HUNDRED AND SIX CASES

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AND

HENRY W. WOLTMAN, M.D.

ROCHESTER, MINN.

Hemifacial spasm is a minor, but distressing, neurologic disease. The records of 663 patients seen at the Mayo Clinic for various unwonted movements of the face have been reviewed; of these, 106 had cryptogenic hemifacial spasm. While we have been primarily interested in clarifying the prognosis, many other aspects of the disease are not generally recognized and will be dealt with.

Our reason for choosing the term hemifacial spasm from the many terms [1] available to describe this condition is simple. The disorder is a spasm that characteristically affects half the face. The alternate term facial hemispasm is incorrect because it is half the face which is affected by spasm, rather than half a spasm of the face.

Before the eighteenth century the term tic was applied to all abnormal movements of the face. André [2] first used the term tic douloureux for grimacing disorders of the face that were accompanied by pain, and the tics came to be separated into those which were painful and those which were not. Trousseau [3] separated from the larger body of painless movements those of a compulsive sort, and Charcot [2] demonstrated the significance of the psychic factor in this type.

Gowers [4] gave a description of facial spasm which leaves no doubt in the mind of the reader concerning his separation of tic from spasm and his segregation of hemifacial spasm from other spasms and convulsions. He stated that the spasm was usually clonic, that the orbicularis oculi was the muscle most often affected, that the frontalis muscle was rarely involved, that spasm of the stapedius muscle may be noted, that the spasm is met with only in adults, that in most of the cases the patients are women, that the spasm bears no relation to hysteria and that emotion and voluntary facial movements increase the spasm. Gowers did not ascribe much importance to reflex causes, as did Romberg,[5] and he discounted the importance of uterine disturbances and of von Graefe's [6] tender points in the distribution of the trigeminal nerve.

CAUSE OF THE SPASM

There has been much speculation on the probable site of the lesion responsible for hemifacial spasm. Previous to the turn of the century, a number of communications reported the occurrence of tumors and inflammations [7] in cases in which facial twitchings occurred, but such a causative agent is not common.

Of interest is the report of Gilbert, Cadiot and Roger [2] describing a dog that had spasmodic twitches of one ear considered to be similar to facial twitches in man. Successive removals of cortex, corpus striatum and cerebellum failed to affect the twitches, but destruction of the homolateral facial nucleus abolished them. Eight years later Habel [8] recorded the case of a woman who did not experience any change in a hemifacial spasm after the development of homolateral hemi-

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1. *Tic convulsif;* reflex facial spasm; hemispasm; the seventh disease; chronic faciospasm; nictitating spasm.

2. Cited by Meige, H., and Feindel, E. C. L.: Tics, and Their Treatment, translated and edited by S. A. K. Wilson, London, S. Appleton, 1907.

3. Trousseau, A.: Lectures on Clinical Medicine, translated and edited with notes and appendixes by P. V. Bazire, London, The New Sydenham Society, 1867, vol. 1, p. 428.

4. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston's Son & Co., 1888.

5. Romberg, M. H.: A Manual of Nervous Diseases of Man, translated and edited by E. H. Sieveking, London, The Sydenham Society, 1853, vol. 1, pp. 290-298.

6. Cited by Russell.[7a]

7. (*a*) Russell, J. S. R.: Facial Spasm, in Allbutt, C., and Rolleston, H. D.: A System of Medicine, ed. 2, London, Macmillan and Company, Ltd., 1910, vol. 8, pp. 638-649. (*b*) Schultze, F.: Linksseitiger Facialiskrampf in Folge eines Aneurysma der Arteria vertebralis sinistra, Virchows Arch. f. path. Anat. **65**:385-391, 1875. (*c*) André-Thomas, cited by Gordon.[10b]

8. Habel, A.: Ueber Fortbestehen von Tic convulsif bei gleichseitiger Hemiplegie, Deutsche med. Wchnschr. **24**:189 (March 24) 1898.

plegia from cerebral vascular disease. The inference to be drawn was that the lesion lay in the nucleus of the facial nerve or distal to it. Babinski [9] expressed the opinion that the lesion is an irritative one in the peripheral course of the seventh nerve.

Some authors [7a] have claimed that the lesion was in the facial representation of the cortex; but, as Russell [7a] said, that hemifacial spasm should be "repeated time after time and year after year, and be confined to the anatomical distribution of a single nerve without further spread, and without causing even temporary paresis following the spasms, is contrary to the best established doctrines of discharging lesions of the cortex. . . . *the most probable view is* . . . that the facial nucleus in the pons is the starting point of the discharges which result in the spasms."

A historically important view [10] is one ascribing the abnormal movements to "reflex irritation." Brissaud [2] proposed that the term "spasm" be limited to "the result of sudden transitory irritation of any point of a reflex arc." He expressed the opinion that "reflex irritation" (in the distribution of the trigeminal nerve) explains a large body of facial spasms. Hunt [11] sponsored the view that the twitching was due to irritation of the afferent system of the facial nerve. Wilson [12] pointed out that afferent stimulation seldom produces the continuous spasms observed clinically but that it is possible that irritation of the facial nerve itself might result in antidromic conduction to the nucleus with the production of some abnormal condition there, which might then produce the spasms. However, he favored the view that direct irritation of the nerve or of its nucleus lay behind the spasm. The tendency for the development of contracture and weakness in the affected side of the face in cases of a long-standing condition led Harris and Wright [13] to the conclusion that the essential lesion is in the lower facial neuron.

9. Babinski, cited by Gordon, A.: Convulsive Movements of the Face: Their Differential Diagnosis; Effect of Alcoholic Injections, J. A. M. A. **58**:97-102 (Jan. 13) 1912.

10. (*a*) Dorrance, G. M.: New Method of Injecting Facial Nerve for Relief of Facial Spasm, J. A. M. A. **67**:1587-1589 (Nov. 25) 1916. (*b*) Gordon, A.: Tic and Spasm of the Face: Differential Diagnosis; Effect of Alcoholic Injections, Tr. Coll. Physicians Philadelphia **34**:313-321, 1912. (*c*) Ross, J.: A Treatise on the Diseases of the Nervous System, New York, William Wood & Co., 1881, vol. 1. Romberg.[5]

11. Hunt, J. R.: The Sensory System of the Facial Nerve and Its Symptomatology, J. Nerv. & Ment. Dis. **36**:321-350 (June) 1909.

12. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

13. Harris, W., and Wright, A. D.: Treatment of Clonic Facial Spasm: (*a*) By Alcohol Injection; (*b*) By Nerve Anastomosis, Lancet **1**:657-662 (March 26) 1932.

OBSERVATIONS

No case was accepted for this study in which there was evidence of a gross pathologic lesion in the posterior fossa or the peripheral course of the facial nerve. We are impressed with the ease with which hemifacial spasm may be differentiated from other twitching disturbances of the face.

Age.—The ages of onset ranged from 17 to 70 years, with a mean age of 45 years and a standard deviation of 12 years. There was no difference in the ages of onset in the two sexes. No report with which we are familiar records a case in which the age of the patient was less than 20 years. One of our patients began to experience the spasms at the age of 17; another, at 19, and a third, shortly after her twentieth birthday.

Sex.—Sixty-four of our patients were women, and 42 were men, thus confirming the observations of other authors [14] regarding the sex distribution.

Side of Face Affected.—In neither sex was one side of the face affected more often than the other.

Location at Onset.—For 7 patients we have no definite information as to the exact location of onset of the twitching. In all but 9 of the remaining 99 patients the muscles of the eyelids were involved early. Sixty-nine patients described their spasm as beginning in the eyelids; 7 patients, in the upper lid, and 18 patients, in the lower lid alone, while in 21 patients the involvement ranged from the eyelids and "quivering in the ear drum" to twitching of the whole side of the face. The reason for the high incidence of early involvement of the lids is not known. Gowers [4] explained the proneness to spasm in the orbicularis oculi muscle by saying that the "motor mechanism of this muscle is more sensitive, in consequence of its energetic reflex action." Oppenheim [15] and other authors [16]

14. Remak, E.: Localized Spasm, in Church, A.: Diseases of the Nervous System, New York, D. Appleton and Company, 1910, pp. 933-959. Gowers.[4] Russell.[7a]

15. Oppenheim, H.: Textbook of Nervous Diseases for Physicians and Students, ed. 5, translated by A. Bruce, New York, G. E. Stechert & Company, 1911, vol. 2, p. 1237.

16. Adson, A. W.: Neurosurgical Treatment of Muscular Spasms and Spastic Painful and Trophic Lesions of the Extremities, S. Clin. North America **13**: 895-904 (Aug.) 1933.

accepted this explanation without modification. In 9 of our patients the spasms did not start in the eyelids, and in 2 of these persons the lids never became involved.

Spread of Spasm.—The spasm usually spreads to adjacent muscles first, perhaps as a result of involvement of the corresponding and contiguously placed nerve cells in the nucleus of the nerve. Possible exceptions were the 9 patients who had only twitching of the orbicularis oculi muscle and drumming, popping or "motor boat" noise in the ears and the 21 patients who had only spasms of the platysma and orbicularis muscles. Thirteen patients eventually suffered from spasms of all the muscles of one side of the face, but, curiously, only 1 of these heard noises in the ear. Sixteen patients of the entire group did not note any spread of the spasm after the onset.

Bilateral Spasm.—Six patients, 5 of them women, had bilateral spasms. The time interval between onset on one side and onset on the other ranged from less than a year to fifteen years. In no patient were the spasms synchronous or symmetric, and in none did the severity or extent of the spasms on the side secondarily involved overtake those on the side primarily involved.

Type of Spasm.—The lay term "twitching" describes the movements rather well. They consist of an intermittent and wholly irregular series of single muscle twitches, coming in rapid sequence and involving but a fraction of the muscle fibers of any one muscle in any one twitch. Twenty-one patients suffered from both twitches and sustained spasm, and in most of the attacks the twitchings increased periodically in frequency and intensity until, at the climax, there was a sustained spasm, lasting from a few seconds to a minute. In 1 patient the onset was with sustained spasm, followed by twitching. Four patients had sustained spasms alone, and the duration of these spasms ranged from a few seconds to five minutes, the length of the spasm being fairly constant in each patient.

Persistence in Sleep.—Twelve patients reported that the twitching had been observed in sleep, and 5 of these patients complained that on occasion they had been awakened by the twitching. Thirty-nine patients had been observed in sleep and reported that spasms were then absent.

Remissions.—Nine patients experienced one or more periods of complete freedom from spasms, lasting from a few weeks to three years. One of these patients experienced a three year period of freedom following gastroenterostomy. Another patient had two years of freedom following refraction and use of glasses.

Provocative Circumstances. — Circumstances said by the patients to increase the severity of the spasms or to precipitate their appearance occurred with the following frequencies: nervous tensions of various sorts, 54 patients; fatigue, 29 patients; voluntary movement of the face, 23 patients; "excessive" use of the eyes, 11 patients; being under observation by others, 9 patients; being with other people, emotion, thinking and talking about the spasm, and menstruation, 4 patients each; concentration, 3 patients; quiet and cold, damp weather, 2 patients each; warm weather, shaving, trying to go to sleep, coitus, talking to "bothersome people," excessive smoking, constipation, loss of sleep and eating sweet and sour foods, 1 patient each. It is apparent that psychic factors have considerable influence on these spasms; yet the influence is of such a character, as will be pointed out later, that it does not cause confusion with the true tics.

Ameliorating Circumstances.—Only 21 patients had discovered circumstances which definitely benefited them. Among these circumstances were solitude, pressure below the lobe of the ear, massage, fatigue, work, relaxation, plenty of sleep, quiet, going away from home, physical activity, coitus, being outdoors and reading an interesting book. Three patients claimed to have some voluntary control of the spasms. The story was the same for all: An effort to relax the face resulted in momentary and slight diminution of spasm.

Neurologic Examination.—In 41 of our patients some abnormality was noted in addition to the spasms. Facial weakness and contracture were observed rather frequently. Weakness was noted in 16 patients, and only on the side of the spasm, except in 1 patient, who had had Bell's palsy of the opposite side several years previously. The importance of contracture has been mentioned in reports[17] dealing with the treatment of the spasm by interruption of the nerve, since the contracture prevents the palsy from being as disfiguring as it might otherwise be.

Partial deafness was another rather frequent finding. In 14 patients hearing was impaired on the side involved by spasm; in 3 patients there was deafness on the opposite side, and 1 patient was somewhat deaf in both ears, but more so on the side of the spasm than on the opposite side.

17. Coleman, C. C.: Surgical Treatment of Facial Spasm, Ann. Surg. **105**:647-657 (May) 1937.

Two patients complained of vertigo. One of these patients had had vertigo for a number of years before the onset of the spasm. Five years later the vertigo disappeared without treatment, but not so the spasm. The other patient had a single attack of vertigo two weeks after the onset of the spasm. Two patients had a homolateral increase of lacrimation.

Two patients had pupillary irregularity; 3, anisocoria; 1, faulty convergence; 2, tremors of the extremities, and 1, cogwheel rigidity of the contralateral arm. Two patients exhibited diminution of the homolateral corneal reflex without demonstrable weakness of the orbicularis muscle. Encountered in 1 patient each were occasional numbness of the homolateral side of the upper lip, mild numbness of the face associated with the more severe twitches, homolateral pathologic plantar reflexes, contralateral pathologic plantar reflexes, contralateral superior laryngeal paralysis, diminution of vibratory sensibility in the homolateral leg, diminution of taste on the homolateral side of the tongue, weakness of the homolateral side of the tongue and diminution of the ankle jerk and of vibratory sensibility in the contralateral leg.

One of our patients was hemiplegic and resembled the patient described by Habel.[8] She suffered from hypertension and began to have left hemifacial spasm at the age of 43 years. Five years later a stroke resulted in severe left hemiplegia, which included the face. The spasm was affected thereby little, or not at all, and when the patient was observed at the clinic a year later the hemiplegia and an unabated hemispasm of the face were still present.

Pathologic Study.—No patient died while under our observation, and therefore we have no necropsy observations to report. Wilson[12] was not aware of any instance in which the brain of a patient with this condition had been subjected to examination by modern pathologic technics. Either investigators in the past did not note anything to account for the spasms, or they encountered gross progressive lesions, such as tumors and aneurysms. Hemifacial spasm is a thing apart from symptomatic facial twitchings due to irritation by such lesions.

Associated Diseases.—It has been suggested[18] that hemifacial spasm is in some instances a manifestation of encephalitis. In 1910 Russell[7a] stated that the condition was rare before the age of 45 years. About half of our patients were less than this age. If encephalitis is a prominent cause, it would explain the high incidence of the condition among our patients in the younger age group, since the pandemic of encephalitis at the close of the war of 1914-1918 affected our group, but not Russell's. One might expect to find, also, a significant time relation in our cases with respect to the years of prevalent encephalitis. Forty of our 106 patients gave a history of having had influenza and the related illnesses in the period from 1919 to 1923. The percentage of patients giving a history of influenza was essentially the same for each half-decade of onset; and there was no peak at a certain interval after the pandemic, as would be expected if this factor were operative. Neither was the age of onset in the group giving a history of influenza different from that of the group as a whole. Only 1 patient gave a straightforward story of hemifacial spasm originating in an episode suggestive of encephalitic disorder.

Forty-one patients had anatomic evidence of arteriosclerosis. Thirty-seven of 92 patients whose eyegrounds were examined had evidence of arteriosclerosis there, but in 7 patients the changes were slight and were not associated with hypertension. Four patients had evidence of coronary or peripheral sclerosis. None of these patients was less than 35 years of age. Fortunately, for our purposes, a previous study[19] had been made of the blood pressures of nearly 1,000 patients who had registered consecutively at the clinic. The accompanying table compares

Percentage of Hypertension Among Patients with Hemifacial Spasm and Among Controls

	Number of Patients	Percentage Having Systolic Blood Pressure of: More Than 144 Mm. Hg	Percentage Having Systolic Blood Pressure of: More Than 159 Mm. Hg
Controls less than 50 years of age	606	9.1	5.4
Patients less than 50 years of age having spasm	39	15.3	5.1
Controls more than 50 years of age	369	37.9	27.4
Patients more than 50 years of age having spasm	61	39.3	32.8

the data for the blood pressures of this random group and the pressures for patients who had hemifacial spasm. It is barely possible that hypertension is more common among patients with spasm who were less than 50 years of age than among other patients of the clinic of corresponding age (who probably have a higher incidence of hypertension than the population at large), but statistically the difference is not significant.

18. Gordon.[10b] Harris and Wright.[13]

19. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, J. A. M. A. **115**:1837-1841 (Nov. 30) 1940.

Remak[14] associated migraine with hemifacial spasm in his account of the condition. Thirty of our patients had headaches of varying descriptions, and for 16 of these a diagnosis of migraine was made. The association remains obscure.

As a condition associated with hemifacial spasm some authors[20] have mentioned trigeminal neuralgia. Three patients in our series had hemifacial spasm associated with trigeminal neuralgia.

A woman, aged 70 when she came to the clinic, had begun to have trigeminal neuralgia of the right side of the face at the age of 55 years. Ten years later there developed rapid and intermittent twitches of the muscles of the right side of the face, which were more pronounced about the angle of the mouth and in the platysma muscle than elsewhere. Section of the posterior root of the affected trigeminal nerve gave complete relief of pain but only slight diminution of the severity of the spasm.

A man aged 21 had had trigeminal neuralgia of the right side of the face for fifteen months. Injection of alcohol into the fifth nerve gave complete relief for four years, when the pain returned in identical form. After about three months he noted slackening of the pain, though he was not undergoing any treatment, and as the pain disappeared there began an intermittent twitching of the right eyelid, which continued without modification for eighteen months.

A woman, aged 60 when she came to the clinic, first had noted twitching of the left eyelids at the age of 45. This continued without significant change for thirteen years, when there began typical neuralgic pains in the mandibular division of the left trigeminal nerve.

It will be noted that in each case the spasm was on the side of the face involved by the neuralgia, a curious association mentioned by Harris and Wright.[13] In the first case the neuralgia antedated the spasm by ten years; in the third case the spasm antedated the neuralgia by thirteen years. It is also of interest that in the first case, even though the pain was relieved, the spasm persisted. The slight improvement of the spasm may be accounted for by the disappearance of the pain and attendant worry, which, like any other discomfort or unnerving experience, may exaggerate an established spasm.

Injuries of the facial nerve of one sort or another have been said to be related etiologically to hemifacial spasm.[21] Movements resulting from faulty regeneration of a damaged facial nerve must be distinguished from hemifacial spasm. Our series included 3 patients whose spasm was preceded by facial paralysis. Two of these patients had the hemifacial spasm on the side that had been paralyzed, but there was nothing about either condition to suggest that the twitchings were of the associated movement type. In the third patient the spasm developed on the side opposite that previously paralyzed, and the faulty regeneration on the side that had been paralyzed verified the patient's story.

Six patients of the series were psychoneurotic. Five patients were rather definite in ascribing the onset of the twitching to psychic causes. These included a broken engagement, persecution as pro-German in 1917 and difficulties with husband and children.

Other diagnoses of associated diseases in the patients of this series were: obesity, 8 patients; infection of teeth, tonsils or prostate, 6 patients; cerebral arteriosclerosis, 4 patients; benign frontal hyperostosis, 3 patients; meningovascular syphilis, 2 patients; latent syphilis, 2 patients, and diabetes, 2 patients. One patient was found to have a concentration of calcium of 8.5 mg. per hundred cubic centimeters of serum but was not benefited by the elevation of the concentration to 12 mg.

DIAGNOSIS

Hemifacial spasm is a condition which, in the great majority of cases, may be diagnosed without difficulty provided the various simulating disorders are kept in mind. Of importance in clinical recognition are the following characteristics: 1. The spasms are of an intermittent twitching nature, such as might be encountered in intermittent faradization of the facial nerve. 2. The eyelids on the side are almost always involved. 3. The spasms are usually unilateral, and when they are bilateral they are not synchronous or equal in extent or severity. 4. The spasms may persist in sleep. 5. The patient does not feel any compulsion to make the movement. 6. The patient is unable to stop the movement by exercise of the will. 7. The patient cannot reproduce the movements voluntarily—especially is he unable to approach the speed with which the fine twitchings occur. 8. Psychic upsets of any sort, fatigue and voluntary movements of the face make the spasms worse. 9. Children do not have hemifacial spasm. 10. The spasms are limited to the muscles innervated by the facial nerve.

Symptomatic spasm due to gross disease in the posterior fossa or along the course of the seventh nerve is recognized by the presence of other signs, in addition to those associated with hemifacial spasm. True tic is distinguished by the involvement of muscles other than those receiving innervation from the seventh cranial nerve, by its frequent onset in childhood, by its variability, by the substitution of one tic for another, by the ease with which the spasm may be reproduced voluntarily, by the fundamental compulsion that the patient feels to make the movement, by the essentially purposive character of the act and by the ability of the victim to

20. Harris and Wright.[13] Oppenheim.[15]

21. Romberg.[5] Russell.[7a] Gordon.[10b] Harris and Wright.[13]

control the movement for a short period. The facial grimace of trigeminal neuralgia is present only with the pain. Facial paraspasm is symmetric, bilateral and predominantly tonic, often affecting the tongue and other bulbar muscles and often ceasing when the patient whistles, sings or chews some object, such as a toothpick.[22] Jacksonian epilepsy may show postconvulsive paresis and gross and clonic contractions, rather than rapid fine twitches and occasional spread of the convulsion. Faulty regeneration sequential to trauma of the facial nerve is recognized by the history of facial paralysis prior to the onset of the spasm and the simultaneous occurrence of slight twitches in some other part of the face associated with voluntary or emotional movements of another part.

TREATMENT

If one were to estimate the number of the various therapeutic procedures recommended at one time or another for hemifacial spasm, it is likely that the figure would compare not unfavorably with a similar total for any other disease of man or beast. Gowers'[4] list is representative. The variety of medicines tried with our series of patients is sufficient evidence that none was of outstanding benefit. One large group of patients received a mild sedative and was advised that more rest was in order. Another group received drugs of the belladonna series, and a few patients, ephedrine, sedatives and vaccines in addition. Other measures included reduction of weight and administration of benzedrine, iodides and diphenylhydantoin (dilantin) sodium.

Patients suffered enough from spasmodic disturbances of the face to undergo surgical operations even before the middle of the nineteenth century,[5] for Guerin and Moreau divided nerves of the face about 1780, while Dieffenbach[5] performed subcutaneous division of the muscle about the orbit, with good results, in a particularly stubborn case of hemifacial spasm in 1841. Nine of our patients underwent surgical procedures of one sort or another, 1 each having retrogasserian rhizotomy, thyroidectomy, injection of alcohol into the facial nerve and injection of procaine hydrochloride into the facial nerve. The procaine was injected preliminary to a proposed injection of alcohol, but the patient was so disturbed by the resulting palsy that nothing further was done. Two patients had diseased teeth and tonsils removed. Three patients were treated by anastomosis of the distal end of the facial nerve with the central end of the spinal accessory nerve.

Information is available for 73 patients on the results of treatment. Six patients died—stroke, cancer and coronary disease being the cause of death of the 3 patients for whom the cause is known. Thirty-nine patients stated that their spasms were unchanged or worse. Twenty-three patients reported moderate improvement; 2 of these are now dead. Only 8 patients were entirely relieved; 1 of these is now dead. Of the 8 patients who were relieved of spasm, 3 were treated by spinofacial anastomosis, with uniformly satisfactory results. Detailed consideration of the technic and of the results to be expected may be found in the communications of other investigators.[23] A variety of treatments were used for the other 5 patients who reported cures. One has been free of spasm for eight years after tonsillectomy and vaccine treatment. One patient experienced relief two months after leaving the clinic under a regimen including reduction of weight, a hot bath each night and administration of salicylates which had been ordered for an unrelated orthopedic condition. One patient reported that she had been free of spasm for three months after the use of thiamine and riboflavin, as ordered by her local physician. One patient had relief from 1933 until his death, in 1940, from injection of alcohol into the facial nerve. One patient's spasm stopped without any treatment. We are inclined to regard the outcome for 3 of these patients as uncertain, since a number of other patients experienced remarkable remissions only to have the spasms recur. It is apparent that little or nothing is to be expected from the use of drugs. Sedatives may modify the disturbance favorably to a slight degree.

Surgical treatment appears to offer the best prospects of obtaining relief and, after conservative measures have failed, should be offered to more patients than has been done. The patient may be told that an operation will relieve the spasm completely but at the cost of a variable period of complete paralysis followed by a longer period during which facial movements are associated with movements of the shoulder or tongue, depending on the operation chosen. If a large portion of the face is involved in the spasm, anastomosis is preferable to injection into the

22. Parker, H. L.: Bilateral Facial Spasm (Paraspasme Bilatéral of Sicard), Arch. Neurol. & Psychiat. **28**:1226-1227 (Nov.) 1932.

23. Gibson, A.: Facial Paralysis, Surg., Gynec. & Obst. **33**:472-489 (Nov.) 1921. Phillips, G.: The Treatment of Clonic Facial Spasm by Nerve Anastomosis, M. J. Australia **1**:624-626 (April 2) 1938. Gilbert, Cadiot and Rogers.[2] Adson.[16] Coleman.[17]

nerve or neurotomy, but the operation should be preceded by a trial of narcotization with procaine to be certain that the patient understands the implications of facial paralysis. Patients who have limited spasms, such as persistent twitching about the eye, are perhaps best managed by some sort of local denervation of the muscles affected, though we have not tried this.

COMMENT

Though abnormal movements of the face may be seen with a variety of lesions in the nervous system, it is altogether unlikely that hemifacial spasm may be caused by lesions in any supranuclear part of the pathway having to do with movements of the face. Our case in which hemiplegia, presumably due to capsular infarction, failed to affect the spasm and a similar case of Habel's constitute evidence that the lesion is not situated in the corticobulbar pathway. It is probable that there are other, uncharted, pathways from the higher centers to the facial nuclei, since certain patients with supranuclear lesions have paralysis of voluntary facial movement but not of emotional movement, and it may be possible that the spasmogenic lesion lies in these other pathways. However, a number of circumstances point rather definitely to the final common path to the facial muscles themselves as the site of the lesion. Perhaps the hardest circumstance to gainsay is the invariable confinement of the spasms to the muscles innervated by the facial nerve. The lesion in hemifacial spasm appears to be progressive, and it is difficult to understand why a lesion situated in the corticobulbar pathway would fail to implicate other muscles in at least a few cases. The frequent weakness and contracture of muscles supplied by the facial nerve speak strongly for disease of the lower motor neuron. Finally, there is the undeniable fact that gross lesions of the lower facial neuron can and do cause a twitching of the face very much like, if not actually indistinguishable from, the twitching of cryptogenic spasm and that the differentiation of symptomatic and cryptogenic spasm must be made on the basis of other evidence of disease of the posterior fossa or the peripheral nerve. The closest approach that can be made to the duplication of hemifacial spasm lies in irregular faradization of the facial nerve itself.

It can be stated with some assurance that the lesion does not lie distal to the exit of the nerve from the stylomastoid foramen, for section at this point and anastomosis with another cranial nerve result in reinnervation of the face with no recurrence of the twitching. Interruption of the facial nerve with subsequent regeneration of the fibers within the facial nerve itself almost always results in return of the spasm.

It appears, then, that the lesion is somewhere between the facial nucleus and the stylomastoid foramen. Thorough histologic examination of this segment of the facial pathway in a victim of hemifacial spasm may settle the question.

CONCLUSIONS

On the basis of the study of 106 patients with hemifacial spasm among 663 patients with pathologic movements of the face of all sorts, the following conclusions are drawn:

1. Women are more often afflicted than men, in the ratio of about 6 to 4.

2. Children do not have hemifacial spasm.

3. Encephalitic illnesses or arteriosclerosis, with or without hypertension, seldom bears a causal relation to hemifacial spasm.

4. The spasms usually begin in one orbicularis oculi muscle and slowly progress to adjacent muscles until, in certain cases, the entire facial musculature is involved.

5. Spontaneous remissions for periods up to three years have been noted.

6. The spasms in almost every case were aggravated by circumstances causing nervousness, fatigue or voluntary movements of the face.

7. No patient was able to stop the spasms by an exercise of the will.

8. Only 5 patients were seemingly cured without resort to surgical treatment, and 3 of these may well be in periods of remission.

9. Spinofacial anastomosis was performed on 3 patients, with satisfactory results in all.

10. There is evidence for the view that the lesion causing this condition is in the facial nucleus or the proximal portion of the facial nerve.

The Mayo Clinic.

METRAZOL AND ELECTRIC CONVULSIVE THERAPY OF THE AFFECTIVE PSYCHOSES

A CONTROLLED SERIES OF OBSERVATIONS COVERING A PERIOD OF FIVE YEARS

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The longer follow-up period and the larger number of patients warrant our present attempt to deal with some of the controversial aspects of convulsive shock therapy not adequately met by earlier studies.

MATERIAL AND PROCEDURE

The procedure is essentially similar to that employed in our first two studies.[1] A comparison is made of the results obtained with treated and with untreated patients with affective psychoses who were seen in private practice in the five years between July 1, 1938 and July 1, 1943. Of a total of 278 such patients, 81 were excluded because of incomplete or complicating data. Follow-up observations were conducted from December 1943 to March 1944, by means of telephone, letter or personal interview. The follow-up period ranged from six to sixty-nine months, with an average of forty months.

Of the 88 patients treated, the first 58 received metrazol and the other 30 were given electric shock therapy. The untreated, or control, group included 109 patients, of whom 43 refused convulsive therapy, 50 had symptoms which were too mild to warrant this treatment and 16 had physical disease which contraindicated use of the method. A comparison of the results for the treated and the untreated patients favors the controls with respect to spontaneity of remissions (table 1), mainly because of the mild character of the illness of many of the untreated patients. All of the treated patients, but only 30 per cent of the control patients, were hospitalized. All our patients, the treated and the untreated alike, were examined and observed over the same period by us.

RESULTS

Immediate and Follow-Up Results of Treatment.

TABLE 1.—*Comparison of Clinical Data for Patients Given Convulsive Therapy and for a Control Series*

	Number of Patients		Percentage of Patients	
	Treated	Untreated	Treated	Untreated
Sex				
Male	33	36	37	33
Female	55	73	63	67
Body build				
Pyknic	58	55	74	63
Asthenic	8	16	11	18
Athletic	12	8	15	9.5
Mixed	..	8	..	9.5
Diagnosis				
Involutional melancholia	22	16	25	14
Manic-depressive depression	51	84	58	77
Manic-depressive mania	15	9	17	9
Severity of illness				
Severe	20	16	23	14
Moderate	67	55	76	51
Mild	1	38	1	35
Previous attacks	49	62	55	57
Prepsychotic personality				
Extraverts	79	94	91	88
Introverts	8	13	9	12
Previous poor health	13	12	16	11
Associated physical disability	19	19	24	18
Positive family history	34	44	41	42
Precipitating episodes	35	41	41	37
Psychoneurotic reaction	18	27	23	24
Somatic delusions	14	7	16	7
Nihilistic delusions	6	5	7	5
Hallucinations	12	11	14	11
Paranoid trends	28	17	33	18
Feelings of depersonalization	8	7	10	7
Erotic reactions	9	3	11	3
Misidentification	7	..	8	..
Catatonic features	4	2	5	2
Destructiveness	9	1	11	1
Violence	5	2	6	2
Fear	39	18	46	17
Poverty of thought with monotonous speech	13	9	15	9
Suicidal tendency	34	35	40	32
Inaccessibility	15	10	18	10
Mutism	1	2	1	2
Lack of insight	46	33	51	30
		Treated		Untreated
Average age		42.5 yr.		43.8 yr.
Average duration of illness before examination		6.4 mo.		9.7 mo.
Average period of follow-up observation		40.0 mo.		39.0 mo.

1. The course of illness was shortened (table 2). This is apparent from the fact that

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1. Ziskind, E.; Somerfeld-Ziskind, E., and Ziskind, L.: Metrazol Therapy in the Affective Psychoses: Study of a Controlled Series of Cases, J. Nerv. & Ment. Dis. **95**:460 (April) 1942; Convulsive Therapy (Metrazol) in the Affective Psychoses: A Controlled Series Covering a Three-Year Period, Bull. Los Angeles Neurol. Soc. **6**:43 (June) 1943.

4 out of each 5 patients attained full remission by the end of the treatment (three to six weeks). Not more than 10 per cent of this number relapsed. Therapeutic superiority is brought into sharper relief if the controls are limited to the most comparable group, namely, the patients refusing treatment, so that the patients with physical contraindications and those with a condition too mild for treatment are eliminated; the results are then full remission for 90 per cent of the treated patients and for 50 per cent of the untreated patients.

2. More remissions took place with treatment than would otherwise have occurred. For the patients die when not given the benefits of convulsive therapy, the illnesses of both the treated and the untreated patients would ultimately go on to the same type of outcome.

This is apparent for our earlier patients (metrazol-treated series and controls), for whom the follow-up period was longest, permitting the largest number of controls to show spontaneous remissions. These patients, all seen in the first three years of the period of study, had a follow-up period ranging from thirty to sixty-nine months, with an average of four and a third years, and the illness of 90 per cent of them, treated and untreated alike, has run its course. For these patients, if the deaths are excluded, the incidence

TABLE 2.—*Results of Convulsive Therapy in Patients with Affective Psychoses as Compared with Status of Controls*

	At End of Treatment: Treated Patients		Follow-Up Observations: Outcome of Observed Attacks: Treated Patients		Follow-Up Observations: Outcome of Observed Attacks: Untreated Patients		Follow-Up Observations: Present Status: Treated Patients		Follow-Up Observations: Present Status: Untreated Patients	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Remission	69	78	79	90	82	75	71	82	68	62
Improvement	16	18	4	5	6	5	4	7	9	8
No improvement	1	1	2	2	8	8	6	7	15	15
Death	2	3	3	3	13	12	4	4	16	15
	88	100	88	100	109	100	85	100	108	100

TABLE 3.—*Results of Convulsive Therapy for Three Types of Affective Psychoses* *

	Treated Patients: Immediate Results			Treated Patients: Follow-Up Results †				Untreated Patients: Follow-Up Results			
	R	I	U	R	I	U	Total	R	I	U	Total
Manic-depressive depression (136)	75%	21%	4%	85%	4%	11%	100%	65%	9%	26%	100%
	40	11	2	45	2	6	53	55	8	20	83
Manic-depressive mania (20)	86%	14%	....	86%	7%	7%	100%	67%	....	33%	100%
	12	2	....	12	1	1	14	4	....	2	6
Involutional melancholia (39)	77%	18%	15%	81%	5%	14%	100%	57%	7%	36%	100%
	17	4	1	18	1	3	22	9	1	7	17

* R indicates recovery; I, improvement, and U, no improvement.
† Under "follow-up results" the outcome is recorded for the original attack under observation; i. e., the effect on recurrent attacks is ignored.

197 patients included, the outcome of the individual attacks under observation was as follows: full remission and improvement in 95 per cent of all treated patients and in but 80 per cent of the untreated patients.[2] These differences are found to be statistically significant (beyond the 1 per cent level on the basis of the chi square test).

3. The treatment prevents death from suicide and exhaustion. This prevention by treatment of deaths which would otherwise take place in the spontaneous course of the illness is to be considered an important therapeutic contribution. Of the total of 20 deaths, 13 in the control series (9 suicides and 4 deaths from exhaustion) and 3 in the treated series (1 suicide and 2 deaths during treatment), were due to the illness or to the treatment. The 2 patients who died during treatment had abnormalities of the electrocardiogram. One died during the first treatment, and necropsy revealed coronary sclerosis. The second died suddenly twenty-four hours after the second treatment, with no apparent symptoms in the interim.

We wish to emphasize that were it not for the fact that a greater number of untreated

2. The results for the patients treated with electrical convulsions (30) were similar to those of the metrazol-treated series (58) and hence were not separated in this study.

of full remissions is 88 and 86 per cent for treated and untreated patients respectively.[3]

4. No essential difference was observed in the therapeutic results for the subtypes of manic-depressive mania, manic-depressive depression and involutional melancholia[4] (table 3).

5. Relapses which followed either immediately or shortly after the termination of treatment arose chiefly from the same factors as those which contributed to therapeutic failure, namely, incomplete treatment, subconvulsive reactions and advanced age (over 60) (table 4). It is desirable to reserve judgment as to the degree of therapeutic improvement until five weeks after the last treatment, since relapses occur rarely, if at all, if full remission has been maintained for five weeks. Failure to follow this routine in our earlier cases was probably responsible for a number of "relapses" in patients whom we should otherwise not have considered fully recovered. The rate of relapse for patients with the disease in full remission should be less than 10 per cent.

6. Recurrences or new attacks of illness were of equal frequency for both the control and the treated series. Fifteen patients, or 18 per cent. of the treated series had recurrence of attacks, as compared with 24 patients, or 21 per cent, of the untreated series. These figures indicate what many observers have already anticipated, namely, that the beneficial effect of treatment is limited to the individual attack and has no bearing on recurrences.

Perusal of the forty-seven statistical reports[5] in the literature appearing since the publication

TABLE 4.—*Analysis of Data on Twenty Patients with Relapses* *

	Relapses		Without Relapse		Total	
	No.	%	No.	%	No.	%
Total number of patients..	20	100	68	100	88	100
Patients with one or more subconvulsive reactions..	17	85	33	49	50	59
Patients with incomplete treatment.....	19	95	12	18	31	35
Patients over 60 years of age.....	6	30	4	6	10	9
Patients over 50 years of age.....	9	45	22	34	31	36

* The immediate results of treatment were as follows: remissions, 8 patients; improvement, 11 patients; no improvement, 1 patient. The follow-up results were as follows: remissions, 12 patients; improvement, 4 patients; no improvement, 4 patients.

TABLE 5.—*Analysis of Data on Fifteen Patients with Recurrences* *

	Patients With Recurrence		Patients Without Recurrence		Total	
	No.	%	No.	%	No.	%
Total number of patients..	15	100	73	100	88	100
Patients with one or more subconvulsive reactions..	11	74	39	53	50	59
Patients with incomplete treatment.....	8	53	23	31	31	35
Patients with relapse after treatment.....	2	13	18	25	20	18
Patients over 60 years of age.....	2	13	4	6	10	9
Patients over 50 years of age.....	5	33	23	34	32	36

* The immediate results of treatment were as follows: remissions, 13 patients; improvement, 2 patients; no improvement, none.

3. Allowance must perhaps be made in this connection for the fact that the study is loaded in favor of the controls, since the control series contained many more patients with mild disease than did the treated series, conditions too mild to warrant convulsive therapy. A trend toward equalization in outcome is, however, definitely indicated.

4. Only the patients with involutional states were included for whom depression was the outstanding symptom. Patients with paranoid states, patients with schizophrenic-like symptoms or patients with conditions otherwise atypical were excluded, since we believe that insulin shock therapy is the treatment of choice for these patients.

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(Footnote continued on next page)

of our last study shows immediate responses to treatment similar to our own. Analysis of 2,777 cases from the same source reveals remissions and notable improvement in 69 per cent, improvement in 18 per cent and no improvement in 13 per cent. Of interest is the remission rate of 56 per cent for the patients with the manic type, as contrasted with a rate of 71 per cent for patients with the manic-depressive depression and of 67 per cent for the patients with involutional melancholia. Our own experience does not bear out the lesser effectiveness of convulsive therapy for the manic type reported in the literature. In our series the results were as good for the manic type as they were for patients with the depressive type. Control studies and long follow-up reports are essentially lacking, so that little has been recorded with respect to the incidence of relapses and recurrences and whether or not the treatment increases the ultimate number of recoveries.

FACTORS CONTRIBUTING TO THERAPEUTIC FAILURE

Subconvulsive Reactions.—As stated in our previous studies, patients who have no subconvulsive reactions during treatment do considerably better than patients having one or more such reactions (tables 6 and 7). Metrazol-treated patients and patients treated with electric shock are alike in this regard. However, introduction of a modified technic which excluded these nonconvulsive reactions [6] with our last 20 electrically treated patients yielded an improved therapeutic response, namely, full immediate remission in 87 per cent.

TABLE 6.—*Relation of Full Remissions to Incidence of Subconvulsive Reactions*

Incidence of Subconvulsive Reactions, %	Patients with Remissions	
	Number	Percentage
0	34	94
25 or less	27	75
Over 25	8	62

Goldman [7] noted that subconvulsive reactions in electrically treated patients had no deterrent effect, though he stated the belief that they are harmful in metrazol therapy. From data published by Kennedy and Wiesel [5y] and Wender, Balser and Beres,[5o'] it appears that subconvulsive reactions had no harmful

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7. Goldman, D.: Personal communication to the authors.

effect, though this is difficult to state because such reactions occurred in practically every case. On the other hand, Kennedy [8] stated that "petit mal" reactions were not only useless but actually harmful. Apparently, the harmful effect of subconvulsive reactions is insufficient to prevent remissions in most cases. Our experience suggests, however, that it does contribute to therapeutic failure and relapse.

Inadequate Treatment.—Failure to administer a full course of therapy covering (1) the acute period of the symptoms, (2) one or two reenforcement treatments and (3) additional treatments in the immediate postdischarge period if early signs of relapses appear is responsible for a large number of therapeutic failures. Confusion as to whether persistence of mild symptoms is residual from the illness or arises as an effect of treatment often makes it difficult to determine whether or not treatment should be continued. The five week post-treatment period of observation is therefore important in this connection.

Age.—Analysis of the results in patients over and under 60 and 50 years of age respectively (table 8) shows a higher rate of recovery for the younger patients. For instance, the immediate rate of recovery for patients under 50 years is 81 per cent, as compared with only 62 per cent for patients over 50 years and 56 per cent for patients over 60 years of age. Similar results were obtained by Fitzgerald.[50] Evans,[5m] although not reporting on the younger age groups, recorded a full remission rate of only 50 per cent for patients over 50 years of age. Cash and Hoekstra [5g] obtained better results with patients above than with patients below 50 years of age.

TABLE 7.—*Effect of Subconvulsive Reactions on Results of Treatment* *

Number of Subconvulsive Reactions	Total	Immediate Results			Follow-Up Results †				
		R	I	U	R	I	U	Relapses	Recurrences
None	41% 36	94% 34	6% 2	.. ..	94% 34	..	6% 2	4% 3	11% 4
One or more	59% 50	70% 35	28% 14	2% 1	86% 43	6% 3	8% 4	34% 17	22% 11

* R indicates recovery; I, improvement, and U, no improvement.
† Follow-up results according to the outcome of the treated attack.

TABLE 8.—*Results of Treatment in Relation to Age*

Age Group	Total Group Distribution of Patients According to Age (Percentage)		Full Remissions (Percentage)			No Improvement (Percentage)	
			Immediate Results:	Follow-Up Results		Follow-Up Results	
	Treated Patients	Controls	Treated Patients	Treated Patients	Controls	Treated Patients	Controls
Cumulative Percentage of Patients up to Age of 70 Years							
Under 50	64	67	81	98	90	1	4
Under 60	89	83	75	93	84	6	9
Under 70	99	96	74	89	80	7	14
Cumulative Percentage of Patients Over Age of 50 Years							
60 and over	10	13	56	56	43	22	50
50 and over	35	29	62	77	52	16	36

HAZARDS OF THERAPY

The unknown quantity, damage to the brain, still remains the major consideration referable to the dangers of treatment. Reports on the working ability of our recovered patients reveal, however, that it is as good as, or even better than, it was in the prepsychotic period. One gains the impression, therefore, that there cannot be any serious impairment to the brain, the reports of their performance being as good as they are. Despite many subjective factors, these clinical impressions are in our opinion as significant as interpretations arising secondarily from laboratory procedures, such as psychologic tests and electroencephalographic records.

SUMMARY

1. For the 88 treated patients the immediate results were as follows: full remission, 78 per cent; improvement, 18 per cent, and no improvement, 4 per cent. The period of treatment was three to six weeks.

2. The follow-up results for these patients, as compared with the results for an untreated

8. Kennedy, P.: Round-Table Discussion on Electric Shock Therapy, read at a meeting of the American Psychiatric Association, 1943.

control group were as follows: full remission in 90 per cent of the treated patients and in only 75 per cent of the untreated patients.

3. In the series of untreated patients there were 9 deaths from suicide and 4 deaths from exhaustion, as compared with 1 death from suicide in the series of treated patients. Two patients with heart disease died during treatment.

4. The incidences of ultimate full remission for our patients with the longest period of follow-up observation (from June 1938 to June 1941) were the same (88 and 86 per cent) for treated and for untreated patients respectively, provided the deaths were omitted from each series.

5. The therapeutic results were the same for all subtypes of affective psychoses: manic-depressive mania or manic-depressive depression and involutional melancholia.

6. Twenty patients had relapses. Of this group, only 8 were classified as having full (?) remissions. Eighty-five per cent of the patients who had relapses had one or more nonconvulsive reactions during treatment.

7. Recurrences (new attacks) occurred with equal frequency in the control and in the treated series, the percentages being 21 and 18 respectively.

8. Full remissions occurred in 94, 75 and 62 per cent of patients having no, one or more and over 25 per cent of subconvulsive reactions respectively.

9. The immediate rate of recovery for treated patients more than 60 years of age was 56 per cent, as compared with the rate of 75 per cent for patients under 60.

10. Working ability after recovery by treatment was as good as and better than prior to the illness. No cerebral damage from the treatment was apparent as judged by the patient's working ability subsequent to treatment.

CONCLUSIONS

1. The benefits of convulsive therapy of the affective psychoses are to be gaged by the reduced period of illness and the greater number of recoveries. The latter effect is due to the decreased number of deaths rather than to any inherent greater therapeutic effect. The treatment in itself is not responsible for any greater incidence of recovery than that which occurs spontaneously if the patient is shielded from death by suicide or exhaustion.

2. The known hazards of treatment for treated patients are less than the hazards for untreated patients. In this study 13 died as a result either of suicide, or of exhaustion.

3. Subconvulsive doses, incomplete therapy and old age are unfavorable factors. Subconvulsive reactions should be avoided.

4. The tendency to recurrences or to new attacks is apparently not influenced by treatment.

5. The possibility of damage to the brain still calls for quantitative evaluation. A margin of safety may be found.

6. This study presents an equal number of control (untreated) and treated patients. More such studies are needed in order to solve adequately the problem of the effect of convulsive therapy of the affective psychoses.

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CARCINOMA OF THE UTERINE FUNDUS WITH METASTASIS TO THE BRAIN

REPORT OF A CASE

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The purpose of this paper is to report what is believed to be a rare case of carcinoma of the uterine fundus with metastasis to the brain. In a review of the literature, we found several reports mentioning the occurrence of metastatic cerebral lesions from a carcinoma of the uterine fundus. However, in no report are the criteria of diagnosis of this lesion given, and we have found no case in which both the primary and the secondary site were examined grossly and microscopically during life.

INCIDENCE OF METASTATIC TUMORS OF THE BRAIN

Meagher and Eisenhardt,[1] in reviewing 1,850 cases of intracranial neoplasm, found that 57, or 3 per cent, were metastatic. Elkington [2] reported 72 cases of metastatic tumors of the brain in a series of 805 cases of cerebral tumor, an incidence of 9 per cent. Dandy [3] estimated the incidence of metastatic cerebral tumor to be 10 per cent of all varieties of tumors of the brain. Adson,[4] however, noted only 2 cases of metastatic tumor in 167 cases of cerebral neoplasm. Globus and Meltzer [5] reported an incidence of 13.5 per cent in a series of 57 cases. Garland and Armitage,[6] in reporting the results of 264 autopsies in cases of cerebral tumor, stated that 12.8 per cent of the tumors were metastatic. In one third of the series the cerebral lesions arose from tuberculoma. When these granulomatous lesions were excluded, the percentage of metastatic tumors in their series became 17.1 per cent. On the basis of these reports, the incidence of metastatic tumors of the brain varied from 1.2 to 17.1 per cent.

ORIGIN OF METASTATIC TUMORS OF THE BRAIN

Metastatic tumors of the brain are not an infrequent complication of carcinoma and sarcoma. Krasting,[7] in examining the tissue in 12,730 cases in which autopsy was done, observed malignant disease in 1,238, or 9.18 per cent. In this series there were 1,078 cases of carcinoma and 160 cases of sarcoma. Examination of the brain was possible in 935 of the 1,238 cases. Of these, 817 were cases of carcinoma, in 39, or 4.7 per cent, of which metastasis occurred to the brain. Of the 118 instances of sarcoma in this series of 935 cases, cerebral metastasis had occurred in 14, an incidence of 12.4 per cent. Rau,[8] in a series of 10,393 autopsies, observed that 3.2 per cent of the carcinomas and 68.1 per cent of the sarcomas had metastasized to the brain. Neustaedter,[9] in examining the records of admissions to the New York City Cancer Hospital, noted metastatic carcinoma to the nervous system in 143 of 6,761 cases, an incidence of 2.15 per cent. Certain neoplasms have a predilection to metastasize to the brain. Carcinoma of the lung and breast are the commonest primary sites. Of 139 cases of meta-

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3. Dandy, W. E.: Metastatic Tumors, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 669.

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7. Krasting, K.: Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystem, Ztschr. f. Krebsforsch. **4**:315, 1906.

8. Rau, W.: Eine vergleichende Statistik der in 5 Kriegsjahren (1914-1919) und 5 Friedensjahren (1909-1914) sezierten Fälle von Krebs und anderen malignen Tumoren am pathologischen Institut des Stadtkrankenhouses Dresden-Friedrichstadt, Ztschr. f. Krebsforsch. **18**:141, 1921.

9. Neustaedter, M.: Incidence of Metastases to the Nervous System, Arch. Neurol. & Psychiat. **51**:423 (May) 1944.

static cerebral neoplasm, Krasting [7] observed that 40 cases, or 25 per cent, followed mammary carcinoma and 29, or 20 per cent, pulmonary carcinoma. Dosquet [10] noted metastasis to the brain in 31.4 per cent of 105 cases of carcinoma of the lung, and Fried,[11] in 16, or 34 per cent, of his series of 47 cases of similar neoplasms. Handley [12] observed cerebral metastasis in 16, or 5 per cent, of 329 cases of primary malignant growths of the breast. Both Krasting [7] and Bailey [13] stated that 50 per cent of all melanotic sarcomas metastasize to the brain.

Elkington [2] reported 72 cases of metastasis to the brain, with the following distribution of primary sites: breast, 18 per cent; lung, 33.3 per cent; gastrointestinal tract, 9.7 per cent; nasopharynx, 8.3 per cent; kidney, 6.9 per cent; urogenital tract, 12.5 per cent; pigmentary structures, 5.6 per cent; miscellaneous areas, 2.8 per cent, and undetermined site, 2.8 per cent. Meagher and Eisenhardt [1] reported 40 cases, with the primary sites as follows: breast, 25 per cent; lung, 35 per cent; gastrointestinal tract, 15 per cent; nasopharynx, 5 per cent; kidney, 2.5 per cent; urogenital tract, 2.5 per cent, and undetermined site, 25 per cent. Dunlap [14] reported 77 cases, the primary sites being distributed as follows: breast, 15.6 per cent; lung, 11.7 per cent; gastrointestinal tract, 13 per cent; nasopharynx, 2.5 per cent; kidney, 15.6 per cent; urogenital tract, 6.5 per cent; pigmentary structures, 6.5 per cent; miscellaneous sites, 18.3 per cent, and undetermined site, 10.3 per cent. In 1 case the cerebral metastasis was reported as primary in the uterus. However, neither the primary nor the secondary site was examined grossly or microscopically to confirm the diagnosis. Neustaedter [9] found 52 cases of malignant metastasis to the brain and reported the primary sites as follows: breast, 27 per cent; lung, 15.4 per cent; nasopharynx, 30.8 per cent; uterus, 5.8 per cent; rectum, 4 per cent; skin, 4 per cent; bladder, 2 per cent; hard palate, 2 per cent; antrum, 2 per cent, and tongue, 7 per cent. This author did not give his criteria for diagnosis of the 3 cases of primary uterine carcinoma with metastasis to the brain, no mention being made as to whether the diagnosis was presumptive or was verified by biopsy, operation or autopsy.

In a review of the literature of secondary metastatic tumors of the brain, we have found the reported incidence of metastatic cerebral tumor with the primary site in the uterus to be low. In the reported cases of these cerebral tumors, no criterion, such as pathologic examination of the primary and secondary sites, either at operation or at autopsy, is given. In the case to be reported the patient had an adenocarcinoma of the fundus of the uterus (fig. 1 *A* and *B*). A total hysterectomy was done, and several months later signs and symptoms of a cerebral neoplasm developed. At operation a metastatic tumor was observed, the sections of which were identical with the sections taken from the uterus (fig. 2 *A* and *B*).

REPORT OF CASE

F. M. M., a white woman aged 48, was admitted to the hospital with a complaint of weakness in the right leg, of nine months' duration, and twitching of the musculature of the right leg, of five months' duration. The family history was noncontributory. The personal history revealed that twenty-two months prior to admission she began to have uterine bleeding, which was diagnosed by her local physician as functional. She was given radium therapy. Thirteen months before admission she began to experience dull pain in the lower part of the abdomen, with radiation to both hips, and had urinary frequency and nocturia. Three months later she became aware of weakness in the right leg. Six months before admission her local physician performed a panhysterectomy. The specimen was sent to this hospital for pathologic examination and was diagnosed as adenocarcinoma of the uterine fundus. Postoperative convalescence was uneventful for two weeks, when she began to have twitching in the right leg, which lasted four to five minutes at a time and was followed by notable weakness of this extremity. Such attacks came on with increasing frequency and severity. Weakness was progressive, and the patient noted that she dragged her right foot while walking. Two weeks before admission to the hospital she had a convulsive seizure, characterized by twitchings in the right foot, which developed into clonic contractions and spread up the right side of the body to involve the right arm and then became generalized, with loss of consciousness. After this attack she experienced a severe generalized headache and numbness of the left side of the face, the right arm and the right leg. Since that time she had had a mild generalized headache, with no nausea or vomiting. There were no visual disturbances or other neurologic symptoms.

Examination revealed normal temperature, pulse and respiration, with a blood pressure of 150 systolic and 100 diastolic. Results of general physical examination were not remarkable. The positive features of the neurologic examination were slight atrophy and spasticity of the musculature of the right calf. The patient

10. Dosquet: Ueber die Metastasenbildung bei primären Lungen-und Bronchialkrebsen, Virchows Arch. f. path. Anat. **234**:481, 1921.

11. Fried, B. M.: Primary Carcinoma of the Lung, Baltimore, Williams & Wilkins Company, 1932, p. 125.

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13. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1933.

14. Dunlap, H. F.: Metastatic Malignant Tumors of Brain, Ann. Int. Med. **5**:1274 (April) 1932.

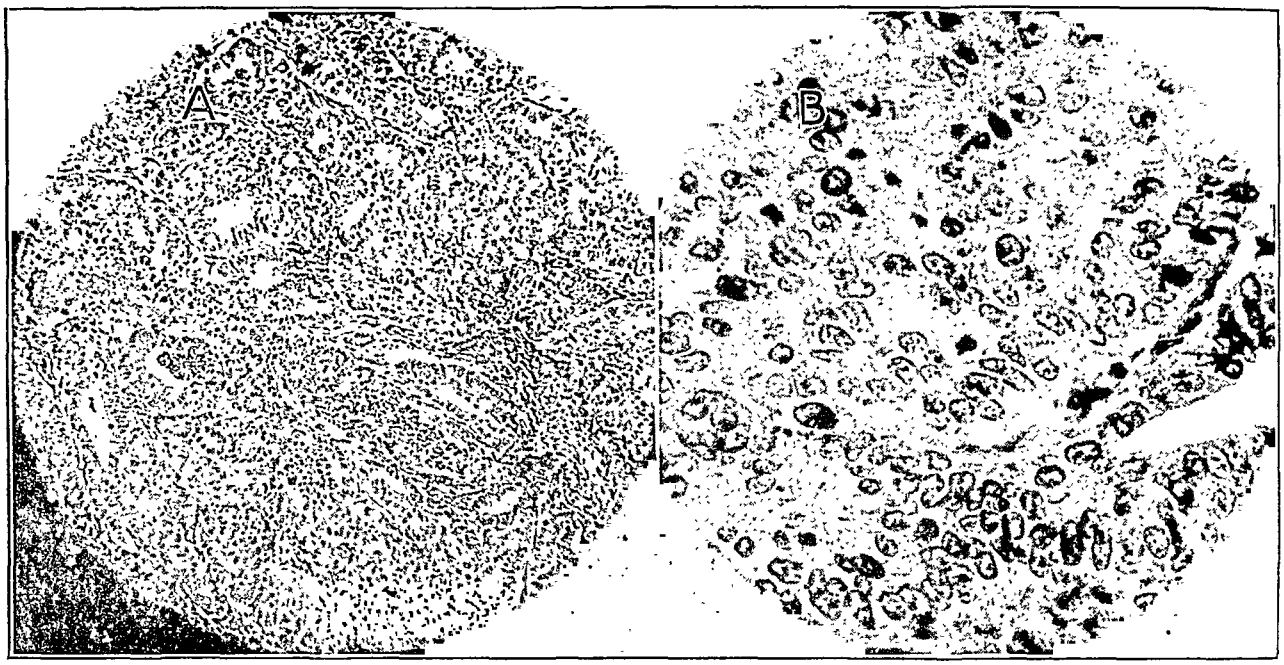

Fig. 1.—Field at left (*A*), × 112; field at right (*B*), × 684. Section of the uterine fundus, showing typical adenocarcinoma. Numerous enlarged and elongated alveoli are lined with several layers of compact cuboidal and cylindric cells, the bodies of which are pale. The nuclei are large and hyperchromatic, and mitoses are seen throughout the section. In several areas there are sheets of disorganized tumor cells, with little tendency to gland formation.

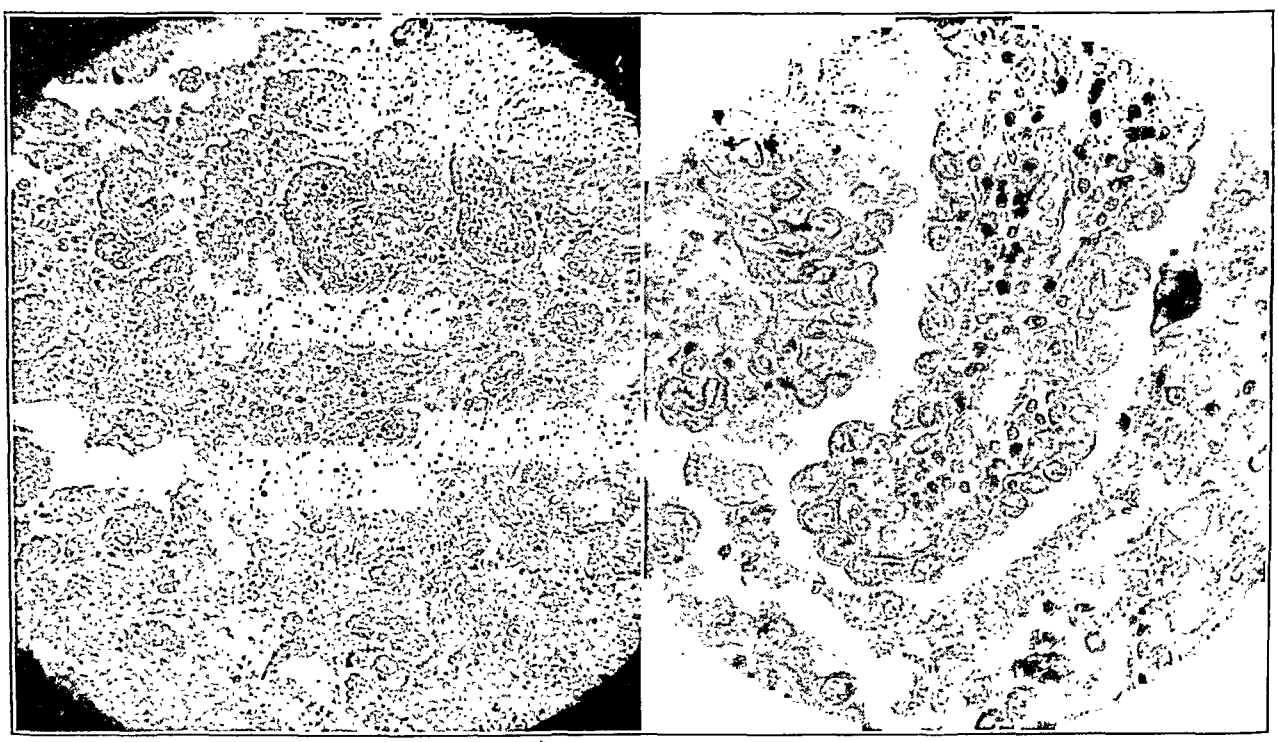

Fig. 2.—Field at left, × 112; field at right, × 684. Section of the brain, showing numerous large tumor cells which are cuboidal and cylindric. The nuclei are large and hyperchromatic, and occasional mitoses are seen. Glandular and papillary formations are striking features. However, some of the cells are scattered in diffuse sheets and cords. In all sections the tumor is infiltrating the brain substance. This tumor is an adenocarcinoma metastatic from the uterine fundus and is similar to the primary uterine carcinoma seen in figure 1 *A* and *B*.

was unable to dorsiflex or to evert the foot. There was also slight spasticity of the muscles of the thigh. Papilledema was not present, and the cranial nerves were not involved. The reflexes on the right side were slightly hypoactive; the abdominal reflexes were absent, and the plantar reflexes were equivocal. Serologic reactions for syphilis gave negative results. The impression was that this patient had a metastatic lesion from the carcinoma of the fundus of the uterus. However, the possibility of a primary cerebral neoplasm could not be ruled out. On her sixth day in the hospital bilateral posterior trephinations, with ventriculographic study, were made; they disclosed flattening of the left lateral ventricle in its midportion, with slight dislocation of the ventricular system to the left, suggestive of a parasagittal tumor on the left side. Dr. Barnes Woodhall performed a craniotomy and exposed a nodular tumor, lying about 2 cm. below the surface of the hemisphere along the midline. The mass was about 4 cm. in diameter and certainly could not have caused the extreme cerebral edema which was present. The tumor was gently dissected until its periphery was quite clear and it was easily shelled out of the brain tissue. However, it was not well circumscribed and did not represent a meningioma, but seemed to infiltrate the brain tissue mesially; on section its appearance immediately suggested a metastatic lesion. No other metastases could be seen or palpated, although it was felt there was a pronounced sense of resistance deep in the white matter toward the ventricle. This tumor involved the motor and sensory cortex on the left side, and pathologic study revealed an adenocarcinoma, the miscroscopic picture being identical with that of the tumor of the uterine fundus. This patient was followed for the two years before her death; at no time did she show any evidence of metastasis other than to the brain.

SUMMARY AND CONCLUSIONS

A patient aged 48, six months previous to admission to the hospital, had undergone a panhysterectomy for an adenocarcinoma of the fundus of the uterus. Two weeks after the operation she began to have twitching, atrophy, slight spasticity and weakness of the right lower extremity, the symptoms being progressive. Two weeks before she was seen at this hospital, a generalized convulsive seizure developed, the onset being focal in character; the convulsion started in the right foot and extended up the right leg, involved the right arm and then passed into the generalized phase. The preoperative diagnosis was probable metastatic tumor to the brain. However, the possibility of a primary tumor could not be ruled out. At operation the patient was observed to have a metastatic tumor to the brain, the pathologic section being identical with that of the uterine carcinoma. We have been unable to find the report of any authenticated case in which uterine carcinoma metastasized to the brain with pathologic examination of the primary and secondary sites during life. There are reports giving the incidence of metastasis of uterine carcinoma to the brain, but no conclusive criteria for that diagnosis were established, as was done in this case.

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CAUSALGIA

REPORT OF RECOVERY FOLLOWING RELIEF OF EMOTIONAL STRESS

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Although it has been apparent that many persons who suffered from causalgia were emotionally unstable, it has seemed doubtful that localized and unilateral autonomic dysfunctions could depend on emotional factors. The case which is reported is of interest in that the full blown syndrome cleared rapidly when the patient was relieved of his emotional distress.

The term causalgia is used to designate a condition, or a group of closely related syndromes, which has received a large number of names.[1] The condition follows injury to an extremity. It is characterized by intense burning pain, which is aggravated into severe paroxysms by trivial physical and emotional stimuli. The skin of the area involved is extremely hyperalgesic, and the slightest movement is painful. These complaints are accompanied by tangible evidence of localized autonomic dysfunction. The skin is red or blue, hot or cold, the state perhaps depending on the duration of the condition, and it may show trophic changes in its texture. The region is wet with perspiration, in contrast to the opposite, normal extremity. There is edema, which may extend into the joint. The muscles are taut, splinting against motion, and there is apt to be muscular wasting. After the condition has persisted for a number of weeks, there may be roentgenographic evidence of osteoporosis, which is greater than would be anticipated from disuse. The pain and hyperalgesia are likely to spread beyond the original limits and in cases of severe form involving the hand may extend into the arm and, finally, into the shoulder girdle. Cases of the late stage tend to be intractable to all forms of treatment, including cervical chordotomy, though medullary tractotomy may be efficacious. The sufferer may become addicted to opiates, may end in an institution for mental disease or may commit suicide.

Causalgia may complicate any one of a wide variety of trauma to an extremity; injuries to the brachial plexus, particularly gunshot wounds; partial lesions of the large nerves; arterial or venous occlusions; fractures; sprains; infected wounds, and, at times, trivial bruises or other minor injuries. It appears certain that a hematoma of the nerve sheath or an arterial occlusion may set up a reflex vasospasm that brings on the chain of symptoms. It is not clear why some simple injuries are followed by causalgia. It has been noted that the condition is likely to occur in persons who had shown previous indications of unstable vasomotor reactivity,[1c] and it has been remarked that some of the patients are unstable emotionally. It is often obscure by the time the patient is studied whether the instability preceded the injury or followed the prolonged suffering.

The nature of the physiologic changes which produce the disability has not been fully clarified. There is agreement concerning the obvious fact that there is localized autonomic dysfunction which causes vasomotor abnormalities. Most investigators consider the phenomena to be secondary to reflex vasospasm induced by stimuli originating in the vessels, nerve trunks or nerve endings in joints. There is evidence, however, that vasodilatation, with distention of the capillaries, and arteriovenous shunts[1b] may play a responsible role. Both vasospastic and vasodilator mechanisms have been invoked to explain the signs shown by the same patient.[1d] The neurophysiologic concepts have been reviewed by Miller and de Takáts.[1a]

A variety of treatments have been advocated.[1] Because of the intractability of the late stage, there is agreement that the abnormal pattern of reflexes must be interrupted as soon as possible. The mild form is said to respond to immobilization, physical therapy and reassurance. Attention is paid to whatever injury or infection exists, and excision of a thrombosed vessel or removal of an organizing hematoma of a nerve sheath may bring immediate relief. Local injections of procaine hydrochloride may be of benefit. Injec-

* Major Lidz is on leave of absence from the Henry Phipps Psychiatric Clinic.

1. (*a*) Miller, D. S., and de Takáts, G.: Post Traumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558 (Nov.) 1942. (*b*) de Takáts, G.: Nature of Painful Vasodilatation in Causalgic States, Arch. Neurol. & Psychiat. **50**:318 (Sept.) 1943. (*c*) White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, ed. 2, New York, The Macmillan Company, 1941. (*d*) Homans, J.: Circulatory Diseases of the Extremities, ibid., 1939.

tions of procaine into the sympathetic ganglia may produce permanent or temporary cessation of symptoms; when only temporary benefit is gained, some form of surgical interruption of the sympathetic fibers is indicated. Long-standing conditions, as has been mentioned, may not be benefited by such procedures.

Attention has been called to the importance of emotional factors. Miller and de Takáts [1a] stressed the importance of "alleviation of fear, anxiety, and reassurance of the patient and avoidance of all factors which may lead to a conscious or unconscious prolongation of a painful syndrome." They stated, however, that "there is no clear-cut evidence that the post traumatic emotional status of a patient can actually influence the local autonomic reflexes originating from an injury." It is with this in mind that the following case is reported.

REPORT OF A CASE

A 20 year old private, with eight months of Army service, was admitted to a general hospital in the South Pacific on Jan. 19, 1944, by transfer from an evacuation hospital. On Dec. 23, 1943, while in a noncombat area, he had wounded himself while cleaning his rifle. His right hand had been over the muzzle when the gun discharged. The bullet shattered the proximal phalanx of the middle finger and caused a compound fracture of the fourth metacarpal and a laceration extending along the proximal portion of the ring finger. The wound had been treated by débridement and the middle finger disarticulated and amputated at the metacarpophalangeal joint. The hand had been kept in plaster for three weeks, and the discomfort and pain suffered were not disproportionate to the injury. After removal of the cast the soldier sometimes complained of pain. On one occasion he sought relief by wrapping his hand about a light bulb. This caused intense pain, unlike anything he had experienced before, but it subsided within a few minutes. He was transferred to the general hospital because contracture of the ring finger necessitated prolonged hospitalization. On arrival at the general hospital, twenty-nine days after the injury, the wound was healing well. The contracture was moderate, and there was little complaint of pain, even with motion. The past history was noncontributory except that he had injured his right shoulder at the age of 16, apparently without fracture. This accident had not been accompanied by symptoms referable to the distal portion of the extremity. Physical examination revealed slight winging of the right scapula and slight limitation of abduction of the arm. No other physical abnormalities were found. The results of routine laboratory tests were all normal.

The hand was treated with progressive exercises, and the wound was handled conservatively. The range of motion in the ring finger increased slowly but steadily, and the wound healed well. Forty-nine days after the injury, when the wound was completely healed, heat treatment was started. During the first treatment, while he was holding the hand under the heat lamp, the soldier again experienced intense pain in the entire hand, which persisted as moderate pain for twenty-four hours. A second treatment on the following day made the pain still worse. The patient's condition altered notably. He complained of constant and intense burning pain in the entire hand, which was intensified greatly by the slightest touch or by movement of any of the fingers. The range of motion in the ring finger diminished, and he became reluctant to move any of the fingers, all of which he held in flexion. The condition continued to grow worse. The hand became flushed and edematous and was always wet with perspiration. The edema spread to involve the entire hand distal to the carpus. The patient suffered severely and slept little, despite sedation. Salicylates and codeine afforded little relief.

For ten days after the onset of the severe pain the condition continued to grow worse. The soldier was reexamined carefully. The blood pressure was 140 systolic and 100 diastolic in both arms, but, aside from the winging of the scapula, the significant findings were otherwise limited to the right arm. Pressure over the right brachial plexus was slightly painful, in contrast to the effect on the left side. Further tests for the scalenus anticus syndrome gave negative results. There was slight atrophy of the muscles of the right upper extremity, including the biceps and the muscles of the forearm, but not more than was to be anticipated from disuse. The wounds of the hand were well healed. There were a few scaled areas on the palm, residue of small "blisters," which appeared to be trophic manifestations. The contrast between the two hands was striking. The left hand appeared normal in contour, color, temperature, moistness and range of motion. The right hand was deeply flushed, wet and cool, and the entire hand, particularly the palm, was edematous. The fingers, aside from the thumb, were held in pronounced flexion. All movements were excruciatingly painful, and only after strong persuasive suggestion was it learned that the fingers could be moved and that strength was good in all except the ring finger. The skin of the hand, especially the palmar surface, was hypersensitive to light touch. The area distal to the wound on the ring finger was hypesthetic.

The diagnosis of causalgia was made, and injections of procaine into the first and second thoracic sympathetic ganglia were considered as a preliminary measure. However, as the patient had shown notable alteration in his behavior after the onset of the pain, and had become moody and ceased to participate in ward activities, psychiatric opinion was sought before active measures were taken.

The patient was seen in psychiatric consultation eleven days after the onset of the severe pain. He appeared worn, moderately depressed and on edge. He was alert and cooperative, and there were no indications of psychotic trends. He complained of being tired, owing to loss of sleep and the constant pain. There were no complaints other than those associated with the hand. His history prior to induction was essentially noncontributory. His parents were living and were in excellent health. His home had been congenial. There had been no neurotic traits in childhood or adolescence, and there were no indications of emotional instability. He had always been congenial and outgoing and had made friends readily. Grade school had been completed without faliures. The patient had then worked on a ranch and had been enthusiastic about training horses. He had married the daughter of the ranch owner a year before his induction and had enjoyed a happy married life. He recalled that after his injury, at the age of 16, when he had fallen from a horse, he had been apprehensive of training horses for a short time but had overcome his fears and had begun to compete in rodeos as a hobby.

The interview soon centered on the origin of the wound and the patient's reaction to it. He stated that he had turned in his rifle when hospitalized with dengue, and the accident had occurred on the day of his release from the hospital. He had given no thought to the possibility that his rifle might be loaded when he had

drawn it from the supply room, as he had never loaded it at any time. He had been wiping the barrel with a rag when he hit the trigger and the gun discharged. When further questions were asked, the soldier started to cry. Ever since he had been interviewed by the psychiatrist at the evacuation hospital, he had realized that it was suspected that he had maimed himself to avoid combat. His unit had been alerted to leave for combat while he had been in the hospital with dengue. The patient was a replacement in a unit that had experienced considerable jungle fighting; after hearing the tales, he had felt somewhat apprehensive, but he denied vehemently having entertained thoughts of injuring himself to avoid fighting. He had not seriously considered the implications that others would place on his injury until some time after his arrival at this hospital, when he had been informed by the ward officer that a line of duty board had found that the injury had not been incurred in the line of duty. He had then become severely upset, as he assumed that it was held that he had shot himself purposefully. He started to worry about what his friends in his company thought of him and what his family would think. He feared that he would be discharged dishonorably from the Army and that his wife would wish a divorce and his parents would not care to have him about their home. He felt that if the line of duty board had found this injury to be wilful, others would form the same opinion. He had considered an appeal but realized that appearances and the testimony were against him. He had tried to cover his feelings but had difficulty in keeping himself from crying, and much of each night was spent in worrying about the situation. The patient was certain that he had been told of the findings of the board on the day before the onset of the acute pain and had slept little that night.

The testimony was injurious to the patient. Circumstantially, it was difficult to see how there could have been a bullet in the rifle unless he had placed it there. Nevertheless, the investigating authority had been impressed, as the psychiatrist at the evacuation hospital had been, with the soldier's sincerity and had found that the wound had been purely accidental. However, a superior authority had reversed the decision after reading the testimony and had found that the injury had not been incurred in the line of duty. It was this reversal of the decision of which the soldier had learned on the day prior to the onset of the causalgia.

The situation was discussed with the patient. It was explained that an investigation by the line of duty board is not a court-martial. It had not been recommended that he be tried by court-martial, which would have been the case if it had been thought that he had wounded himself wilfully. The implications of the decision of the board were not minimized, but his attitude toward it, particularly his hopelessness and resentment, was discussed. It was a situation which, even if he considered it a miscarriage of justice, was understandable and must be met. Considerable discussion was devoted to his concerns over the attitude which he feared his family would adopt. At the termination of the interview the soldier was greatly relieved and stated that it was good to be able to discuss the worries he had been hiding. On the same day the surgeon in charge of his care continued the discussion, reassuring the soldier of faith in his character and stressing the need for the patient to regain his self esteem and face the problem. He was given the suggestion that the hand would begin to improve. The patient slept soundly that night for the first time since the pain had started and on the following morning reported that his hand hurt less. No objective changes were visible, but the soldier was encouraged to use the hand as much as possible.

On the afternoon of the day following the psychiatric interview, the patient was questioned after an intravenous injection of sodium pentothal. He told the same story as on the previous day and denied that he had sought to escape combat. While still in a hypnotic state from the barbiturate, he was given the suggestions that the pain would lessen and that the range of motion in the hand would increase from day to day.

The patient continued to sleep well with little, or no, sedation, and there was a striking alteration in his attitude and behavior. He again became friendly with other patients, kept working at the movement of his fingers and rarely complained of pain. Three days after the interview he reported that the pain was moving outward from the palm toward the periphery in progressive fashion, as had been suggested. Diminution in the flushing and sweating could be noted. A week after the interview the hand was painless, and all indications of vasomotor abnormality had disappeared; the color and sweating were similar to the condition of the left hand, and the edema and hyperesthesia had gone. The patient appeared cheerful, and he was working at occupational therapy to improve the range of motion in the ring finger. Brief daily discussions were mainly given to reassurance and encouragement.

Heat therapy was tried again after another week to learn whether it would precipitate a recurrence of the pain. The patient reported that the treatment was painless and that he believed it improved motion. Physical therapy and heat were given daily thereafter. Improvement in the range of motion of the ring finger continued steadily, and six weeks after the onset of recovery but slight limitation of extension remained and strength was excellent. The absence of the middle finger caused him no inconvenience. After several discussions concerning the situation, the soldier was returned to his unit for full duty. He had decided that, despite his reluctance to return to a unit in which he believed he was held in disgrace, it would be best for him to prove himself in combat and regain the respect of his friends.

COMMENT

The case appears to have contained all the essential components of the causalgia syndrome. The injury involved joints and peripheral nerves and resulted in the amputation of a finger. There was clear evidence of localized autonomic malfunction, as shown by the change in the color of the skin, edema, sweating and early trophic disturbance. There were acute hyperalgesia and constant burning pain, which was exacerbated by slight stimuli. The least movement was considered unbearable, and the fingers were kept motionless in a flexed position.

Recovery started immediately after the patient was helped with the handling of his emotional problems, which were resultant on the circumstances surrounding the injury. It seemed unlikely that the improvement was coincidental, as the alteration in his attitude was as pronounced as the changes in the hand. It is deemed of interest that the therapy was extremely simple. It did not involve basic personality traits or a change in actual situations or an investigation of the possibility of unconscious motivation of the accident. The situation was altered by clarifying it and by changing the soldier's attitude toward the circumstances. The catharsis of his pent-up

emotions afforded considerable relief, which was furthered by the help given him in regaining his self esteem. The suggestion given under the influence of sodium pentothal and the more casual suggestion made daily were believed to have been beneficial because the ground had been cleared by discussions of his concerns. It was fortunate that psychiatric help was offered early, before the changes had time to become fixed, and that the emotional trauma did not involve matters that were basic to his personality structure.

Although it has been clear from the literature that many persons suffering from causalgia were emotionally unstable, there has been doubt that such unilateral and localized difficulties, in contrast to more generalized autonomic disturbances, could depend on emotional influences. The present case offers striking evidence that the emotional state of the patient can, perhaps in conjunction with local stimuli arising from the traumatized area, influence the local autonomic reflexes in a single extremity.

SUMMARY

In a case of causalgia, with a typical syndrome, recovery followed promptly on simple psychotherapy.

EROTOMANIA (NYMPHOMANIA) AS AN EXPRESSION OF CORTICAL EPILEPTIFORM DISCHARGE

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MADISON, WIS.

Relatively little is known in regard to the representation of the sacral segments of the cord in the cerebral cortex of man. Penfield and Boldrey [1] (1937) recorded sensation in the opposite side of the penis following cortical stimulation but obtained no motor responses. They pointed out that the rarity of responses in the lower sacral and genital regions may be due to the comparatively small number of stimulations which the neurosurgeon is able to perform within the central fissure, or possibly to a false sense of modesty on the part of the patient. Scarff [2] (1940) observed contraction of the anal sphincter in 1 patient after electrical stimulation of the medial surface of the cerebral hemisphere.

In contrast to the paucity of observations in man, the representation of the sacral segments has been worked out with considerable precision in the cortex of the monkey (Woolsey, Marshall and Bard,[3] 1942; fig. 1). It is reasonable to suppose that the genitalia and other perineal structures in man have a similar sensory representation in the cerebral cortex of the paracentral lobule on the medial surface of the hemisphere. A priori, one would expect this area to be the occasional site of an epileptogenic lesion manifesting itself by a sensory jacksonian seizure with its onset in the genitalia. No such case had, however, come to my attention until the one presently to be discussed, nor have I been able to find a similar instance recorded in the literature.

Read at a meeting of the Chicago Neurological Society, April 11, 1944.

From the Department of Surgery, University of Wisconsin Medical School.

1. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**: 389-443, 1937.

2. Scarff, J. E.: Primary Cortical Centers for Movements of Upper and Lower Limbs in Man, Arch. Neurol. & Psychiat. **44**:243-299 (Aug.) 1940.

3. Woolsey, C. N.; Marshall, W. H., and Bard, P.: Representation of Cutaneous Tactile Sensibility in the Cerebral Cortex of the Monkey as Indicated by Evoked Potentials, Bull. Johns Hopkins Hosp. **70**:399-441, 1942

REPORT OF A CASE

Mrs. C. W. was first admitted to the Wisconsin General Hospital on May 18, 1939, at the age of 55, and, after study, was discharged on June 9, 1939, with a primary diagnosis of nymphomania. In the following account of her history I shall quote her own description of the sensation whenever possible.

The patient stated that she had always "enjoyed sexual intercourse," but since the age of 43 she had become increasingly "passionate." At night she would awaken with a feeling of being "hot all over," as if she were having coitus. This sensation would last about five minutes. After the first four or five weeks, it became more frequent until a year before admission (at the age of 54), when it decreased but still occurred every afternoon. Her husband suffered from hyper-

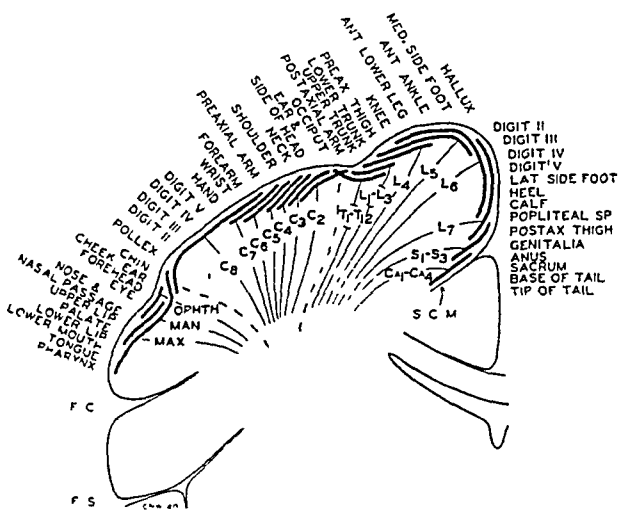


Fig. 1.—Reproduction of cortical sensory chart in the monkey (Woolsey, Marshall and Bard,[3] fig. 14). In this figure, *C, T, L. S* and *Ca* with their subscripts refer to specific dermatomes of projection. *F.S.* is the sylvian fissure; *F.C.*, the central fissure; *S.C.M.*, the callosomarginal sulcus; *MAX.*, the maxillary distribution; *MAN.*, the mandibular distribution, and *OPHTH.*, the ophthalmic distribution. Note the responses obtained from the perineal regions.

tension and finally had a stroke in December 1938! She stated that when he could not satisfy her he made "nasty remarks and left her to herself." When the "hot feeling" was pronounced, she could obtain relief from a lukewarm tub bath, followed by packing of the vagina with cracked ice.

Ten years before this admission (i. e., about two years after the onset of the nymphomania) she suddenly felt unable to speak during one of the "hot spells"; she became "tight all over" and had "jerking movements"

of the left leg and the left side of the abdomen. At times there was a feeling of movement without actual movement. These attacks lasted for twenty minutes and recurred daily for a period of two years, but later they recurred only once every six months. At first she laughed and cried when she had the attacks, but she said she was not so hysterical later because various physicians had warned her that she would be put in a straight jacket if she did not control herself.

When the nymphomania first began, she had "an affair" with another man; but when her husband discovered it, she never again tried to satisfy herself in this fashion. When she used alcohol or perfume she thought her symptoms were accentuated. She joined the Mormon church and felt that "their strict rules saved her." Sexual relations with her husband stopped when he had the stroke. The nymphomania and her husband's impotence alienated the affection of both her husband and her children, of whom she had ten, ranging in age from 18 to 37 years.

Her menses began at the age of 13 years and occurred regularly every twenty-eight days, with an abundant flow lasting seven days. For six months before the first admission to the hospital, at the age of 55, the menstrual flow had become more scanty and irregular, and she had hot flashes. There was no chronologic relation between these menopausal symptoms and the nymphomania.

Physical examination revealed a well developed, somewhat obese, white woman. The blood pressure was 140 systolic and 90 diastolic. There were a well healed thyroidectomy scar, numerous areas of vitiligo over the chest and brown pigmentation of the eyelids. Dr. M. J. Thornton reported that pelvic examination revealed nothing abnormal except for a first degree cystocele and rectocele. Cervical smears were negative for gonococci and yeast, but Trichomonas was present. Biopsy of the endometrium showed a normal follicular reaction. Roentgenograms of the chest and sinuses revealed nothing abnormal. Hypertrophic arthritis of the cervical portion of the spine was observed. Roentgenographic study of the left shoulder showed nothing abnormal. No other pertinent observations were recorded at this time. In view of the fact that the nymphomania was her major symptom, roentgen ray therapy (four treatments of 200 r each) was given to stop ovarian function. The patient was discharged on June 9, with a diagnosis of nymphomania and first degree rectocele and cystocele.

The patient was readmitted to the hospital on Feb. 23, 1940. Her daughter stated that since discharge there had been no sexual irregularities as far as was known but that she still had an abnormal desire for intercourse. In September 1939 she had a severe and profuse menstrual period. The same month she had convulsive seizures, which always began in the left leg after an aura consisting of a "passionate feeling." During these attacks, she bit her tongue; her eyes rolled back in her head, and her body stiffened out. The first major seizure was followed by a partial paralysis of the left side of the body. Phenobarbital, ½ grain (0.032 Gm.), had been efficacious in cutting down the number of seizures. The patient's daughter stated that her mother had been nervous and at times irrational and unreasonable. She had threatened to take her own life on several occasions. The patient had no further major seizures from September 1939 to February 1940; however, she had several slight attacks, during which she shook all over for several minutes. She had menstrual periods in December 1939 and February 1940.

In addition to the lesions previously recorded, physical examination revealed a large, soft, movable mass, probably a lipoma, over the right clavicle; prominent inguinal adenopathy; apical and basal systolic murmurs, and a blood pressure of 126 systolic and 70 diastolic. Neurologic examination disclosed paresis of the entire left upper extremity and, to a lesser degree, of the lower extremity. The face was not involved. Reflexes were exaggerated on the left side, but a Babinski sign could not be elicited. There was no involvement of the tongue or face. The fundi were normal, showing relatively little sclerosis. The results of pelvic examination were essentially normal.

Routine laboratory studies revealed normal urinary constituents, a hemoglobin concentration of 13.4 Gm. per hundred cubic centimeters and a white blood cell count of 7,250, with a normal differential count. The sugar content of the blood was 86 mg. and the nonprotein nitrogen 31 mg. per hundred cubic centimeters; the Wassermann reaction of the blood was negative. A lumbar puncture revealed an initial pressure of 236 mm. of water. The Wassermann reaction of the cerebrospinal fluid was negative; the colloidal gold curve was 1222100000; the reaction for globulin was faintly positive, and the cell count was zero.

The report of the roentgenographic examination of the skull (Dr. Lester Paul) was as follows: "The sella is normal in size, but the posterior portion of the floor and the posterior clinoid processes appear decalcified and thinned. The anterior clinoid processes are intact. The cranial bones elsewhere are of normal appearance. There is no abnormal intracranial calcification or other localizing evidence of intracranial neoplasm. The changes noted in the sella, however, are suggestive of erosion from extrinsic pressure." A roentgenogram of the chest showed no significant change from the film taken the previous summer. A roentgenogram of the dorsal portion of the spine revealed slight scoliosis to the left side and slight hypertrophic change throughout that portion of the spine. There was an old fracture in the posterior arc of the left eleventh rib, with evidence of callus.

It was the opinion of the medical and psychiatric staff at this time that the signs presented by the patient were the residuals of a vascular lesion in the right motor cortex, but that the presence of a neoplasm had not been entirely ruled out. In view of the patient's continuing menses, it was felt advisable to provide several more roentgen ray treatments to the ovaries; and, after consultation with the department of roentgenology, she was given four additional treatments, consisting of 200 r each. In addition, she received physical therapy to the left shoulder and noted some improvement under that regimen. Thiamine hydrochloride, 50 mg. daily, was provided, as well as theophylline ethylenediamine, 1½ grains (0.097 Gm.) four times a day. The final diagnoses at the time of discharge, on April 22, 1940, were cerebral vascular accident with symptomatic grand mal epilepsy, nymphomania, vitiligo, lipoma and menopausal syndrome.

Because of a gradual increase in the left hemiplegia, the patient was readmitted to the hospital on June 18, 1943. During the two year interval since the previous admission she had spent most of her time in a nursing home. The symptoms of nymphomania had persisted. There had been a slight show of blood on two or three occasions during the year. The patient said that the roentgen ray therapy to her ovaries had not helped her menses, and she wished that she had left her husband and married another man "who could take care of her" (intercourse). At this time she described the "passionate feeling" as being accompanied by staring of the eyes so that she could not move them, and then by feeling that the yolk of an egg was running down

her throat (apparently a postnasal discharge). She also noted that when she blew her nose the left big toe drew upward.

Examination by Dr. Mabel Masten on June 21 revealed that there had been a gradual increase in the left hemiparesis which originally followed epileptic seizures, in 1939. The left side of the face was weak, and the left arm and leg had become spastic, with contracture of the left shoulder joint. A grasp reflex and a Wartenberg sign were elicited on the left side. There was wrist and ankle clonus. Dr. Masten expressed the belief that the findings strongly suggested a cerebral tumor, such as a slowly growing meningioma.

Lumbar puncture, with the patient recumbent, revealed an initial pressure of 250 mm. of water. The spinal fluid contained no cells, and the protein content was 35 mg. per hundred cubic centimeters; the colloidal gold curve was normal, and the Wassermann reaction was negative. Ophthalmoscopic examination showed normal fundi. Roentgenographic examination of the skull showed no change since the previous examination, when there were thinning and decalcification of the dorsum sellae. In the occipital region an area of translucency 1 cm. in diameter was thought to represent a congenital ossification defect, since it was midline in position and had not changed over a period of years. The patient had a jacksonian seizure on the left side on the day prior to operation; this was similar to the seizures previously described.

Pneumoencephalographic study, carried out on July 1, 1943, revealed a shift of the midline structures from right to left, with flattening of the roof of the right lateral ventricle to a level at least 1 cm. lower than that of the left lateral ventricle (fig. 2). There was absence of air in the subarachnoid channels over the right hemisphere except for filling of the island of Reil, which was lower in position than the corresponding structure on the left side. It was concluded that there was an expanding, space-occupying lesion in the right parietal parasagittal region.

An osteoplastic craniotomy was performed in the right parietal region, with the use of local anesthesia, on July 1, 1943. The tumor was noted at the upper end of the rolandic sulcus between the medial surface of the hemisphere and the falx (fig. 3). The tumor was completely removed, and its area of attachment to the falx was coagulated with the Bovie unit.

On microscopic examination (fig. 4) this tumor was observed to be composed of numerous endothelial cells and small vascular channels, some of which were occluded by a hyaline material. There was no variation in cell size and no mitotic figures. A diagnosis of hemangioma was made by Dr. W. H. Jaeschke.

Stimulation of the cortex with the thyratron stimulator gave slight responses in the arm and face area but none in the leg area. The patient was not sufficiently cooperative for elicitation of any sensory responses. The postoperative course was without any unusual incident except for the occurrence of a single local clonic seizure involving the left arm alone on the fifth postoperative day. The patient occasionally complained of pain in the left arm and leg, which was felt to be due to contractures following the long-standing hemiplegia The pain improved with physical therapy. The subjective symptoms of nymphomania were present on only one occasion after operation, from which her convalescence was rapid and otherwise uncomplicated.

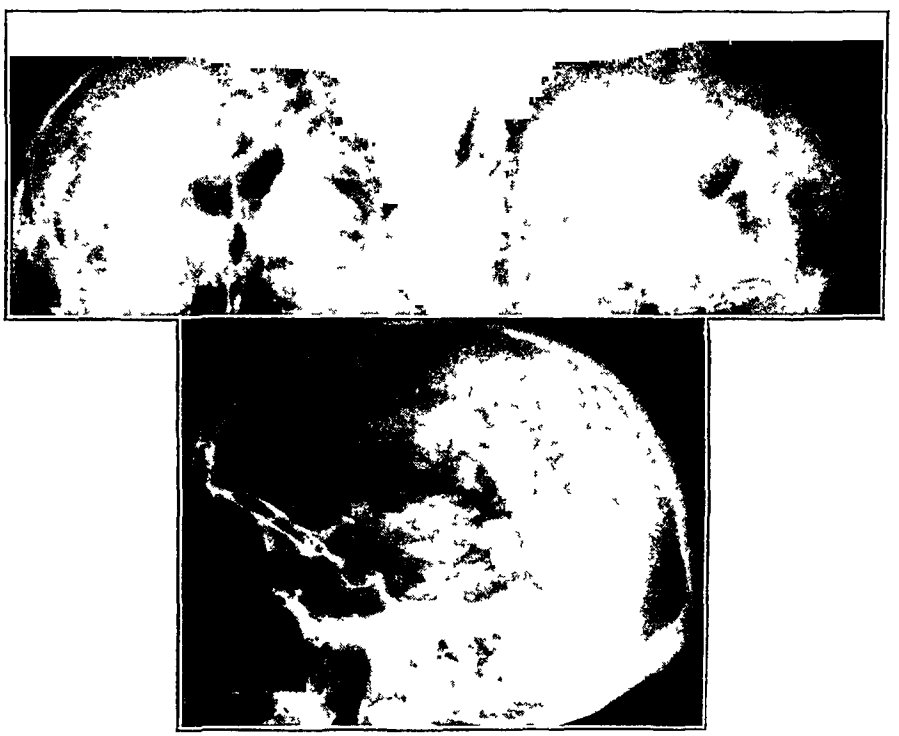


Fig. 2.—Pneumoencephalograms of the patient, showing the location of the parasagittal tumor.

A Rorschach test, done on the thirtieth postoperative day by Dr. M. Harrower-Erickson, was reported as follows: "The record is within normal limits. There is no indication whatever of the typical organic personality pattern. Another surprising feature is the speed with which the responses are made and the number of original responses that are given. There are no unusual sexual responses. Evidence of good contact with the environment and adequate control is present. While the record is not one of a particularly intelligent person, there is no suggestion of intellectual deterioration."

Partial left hemiplegia persisted when the patient left the hospital after operation. She wrote frequent letters revealing that she was resentful of the use of roentgen ray therapy to the ovaries, and she also expressed fear because of persistent paralysis that she might have another cerebral tumor. In July 1944, a year after removal of the tumor, she returned to the hos-

pital for examination. She had had no headaches and no convulsive seizures. Once, while helping to lift another patient, she had noted shaking of the left arm, which was interpreted as clonus. When asked if she had had any "passionate spells" since operation, she said, "No, I haven't had any; they were terrible things." Closer questioning revealed that she had what she interpreted as normal sexual desire, but she insisted that this did not have the insistent character and uncontrollability of the previous attacks. The strength in her leg had improved so that she was able to walk well, but the hand had shown little improvement.

She had had no urinary difficulty; her appetite was good, and she had had no vertigo, tinnitus or syncope.

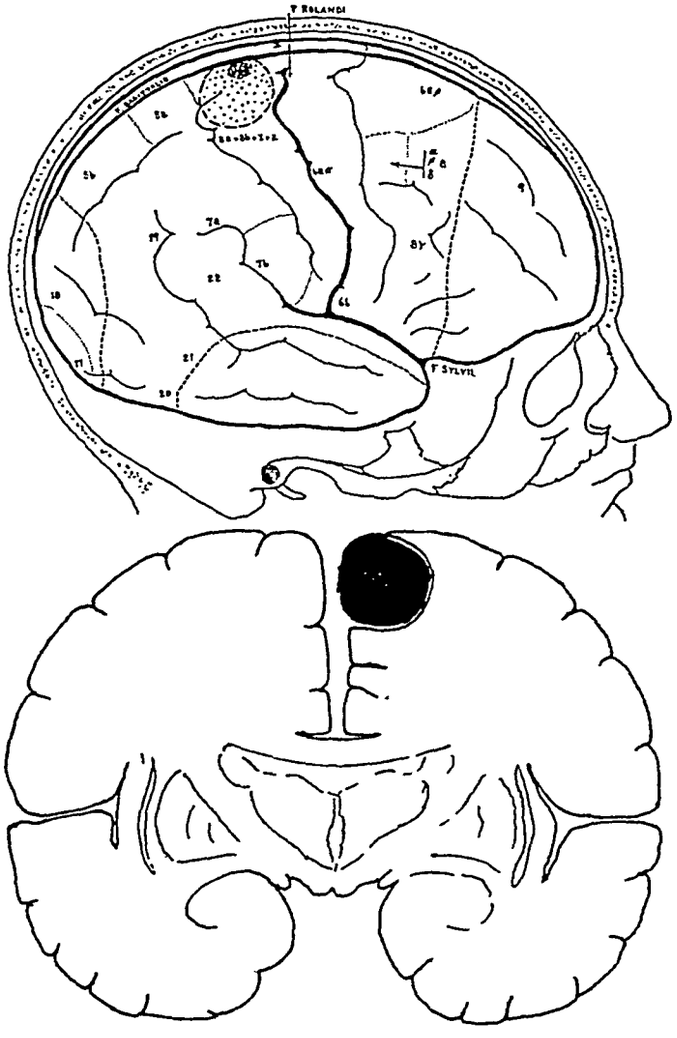


Fig. 3.—Diagrams illustrating the location of the neoplasm as disclosed at operation.

She had not had any menstrual bleeding except for a slight show on two days in the autumn of 1943.

Examination at this time showed that the patient still had spastic left hemiplegia, which was complete in the arm and partial in the leg. There were astereognosis in the left hand and loss of skin writing and position sense. The wound was well healed, and the cranial nerves were normal.

COMMENT

In this case nymphomania was clearly the result of a tumor which caused excitation of the topical projection of the genital structures on the medial surface of the cerebral hemisphere. For two years the patient presented no symptoms other than the nymphomania. The significance of this symptom was only evident when the same sensory experience was followed by jacksonian seizures and, finally, by progressive hemiplegia.

The sensory representation of the genitalia has been demonstrated in monkeys to lie in the paracentral lobule at the upper lip of the callosomarginal sulcus (fig. 1; Woolsey, Marshall and Bard [3]). In my patient electrical stimulation of the cortex gave a few responses in the arm area of the precentral gyrus but was not satisfactory in the immediate vicinity of the lesion because of the depression of function, caused no doubt by removal of the vascular tumor. The tumor was attached to the falx and impinged on the paracentral lobule on the medial surface of the hemisphere just above the sulcus cinguli, an area homologous to that which contains the sensory representation of the genitalia in monkeys.

The patient's description of her initial sensation did not enable me to localize it to any particular portion of the genitalia, nor was it described as a numbness or tingling similar to the usual sensory seizures. It seemed to be mainly contralateral to the cortical lesion. To quote the patient: "These spells are just the same as ordinary intercourse, but only on the left side. They are relieved for a while after intercourse, but I could have intercourse all the time without very much relief." She denied any attempt at masturbation or recent homosexual activity. The patient did not distinguish this sensation from the normal, and it led her to seek sexual intercourse. Although this "passionate feeling," as she called it, had the usual agreeable qualities of the normal, its frequency and uncontrollability, and the fact that it was later followed by a jacksonian epileptic march, made it annoying and distasteful to her.

Thorough and repeated gynecologic examinations failed to reveal any peripheral cause of the nymphomania. My colleagues in gynecology tell me that local changes in the pelvis are rarely responsible for this symptom and that a patient with this disturbance is usually referred to the psychiatrist.

According to Forel [4] (1926), erotomania (nymphomania) is especially noted with acute mania and with the early stages of dementia paralytica and senile dementia, as well as temporarily or permanently with other psychoses. It is worthy of note that my patient showed no psychotic traits either in the Rorschach test or on clinical examination. Her malady might well have been

4. Forel, A.: The Sexual Question: A Scientific, Psychological, Hygienic and Sociological Study, ed. 2, translated by C. F. Marshall, New York, Physicians and Surgeons Book Company, 1926.

expected to give rise to indirect psychologic changes, as it did.

Many of the recent papers on nymphomania discuss the effect of endocrine preparations, but there is no consensus in regard to the results with the various glandular substances. In the present case artificial menopause induced by irradiation of the ovaries, only partially effective, it is true, had no influence on the nymphomania; in fact, the condition progressed steadily and ceased only after the removal of the cerebral tumor. That the nymphomania was more severe in association with the menstrual periods was no doubt due to changes in the neoplasm as the result of premenstrual edema. The accentuation of symptoms due to cerebral tumor in this way is well known. The late onset of the menopause suggests the possibility that the delay was caused by the abnormal or excessive innervation of the genitalia.

Although the lesion was no doubt close to the cortical representation of the urinary bladder, the patient at no time had any urinary difficulty, owing perhaps to bilateral innervation of this structure. This particular tumor no doubt varied greatly in size because of its vascular nature. In fact, the pneumoencephalogram suggested the presence of a much larger tumor than was actually removed at operation, and one can assume that this was due to a variation in its size from time to time.

Whether the type of lesion presented by this patient represents an extreme rarity among patients with symptoms of nymphomania or whether there are other, similar, cases which have gone unrecognized is impossible to ascertain until psychiatrists and neurologists direct their attention to the possibility of the existence of an organic lesion in the sensory area of the cortex in patients with erotomania (nymphomania or satyriasis). Either a tumor or an atrophic lesion might be expected to produce such a symptom if it caused irritation of the area of the sensorimotor cortex representing the genitalia. Finally, one should not necessarily expect to encounter a large tumor as the cause, for even a small cicatrix or vascular lesion might theoreticaly give rise to an epileptiform discharge in this region.

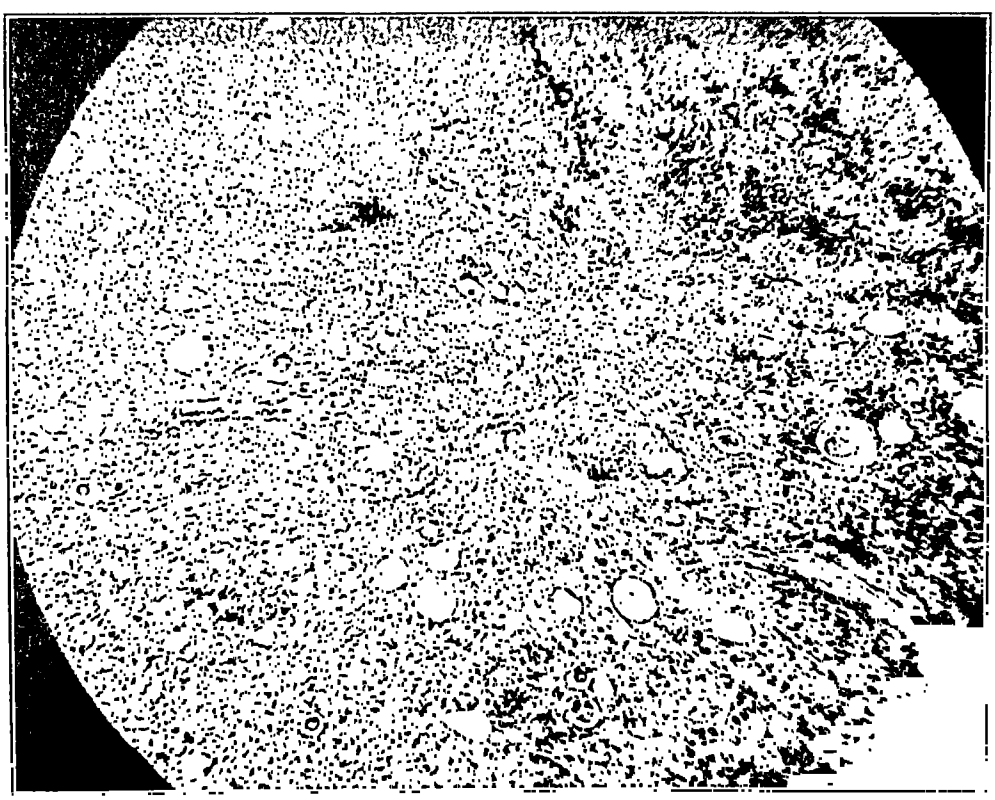


Fig. 4.—Photomicrograph of encapsulated hemangioma removed at operation.

SUMMARY

Erotomania as the initial manifestation of a cortical epileptiform discharge has not previously been described. In the present case the patient began to manifest nymphomania, which occurred in paroxysms of short duration, at the age of 43 years. Two years later these spells of nymphomania served to usher in typical jacksonian seizures, spreading first to the left lower extremity. With repetition of the focal seizures postictal paralysis supervened. Examination revealed the presence of a neoplasm, causing excita-

tion of the topical projection of the genital structures in the right paracentral lobule. A year after operative removal of the neoplasm the patient no longer exhibited nymphomania.

DISCUSSION

DR. VICTOR E. GONDA, Chicago: The lesion being so near the paracentral lobule, I should like to ask whether this patient ever had any subjective or objective urinary difficulties.

DR. RALPH C. HAMILL, Chicago: I had a patient, a girl aged 19, with a tumor of the pineal gland the size of a small olive. She had definite nymphomania. I wonder whether the pineal gland or the paracentral lobule was irritated by the tumor.

DR. THEODORE C. ERICKSON, Madison, Wis. My patient did not have any urinary complaints. I do not see how a pineal tumor could come into contact with this region of the cortex. My associates and I have seen several patients with lesions of the frontal lobe who exhibited increased libido, and I always assumed it was due to lack of inhibition.

NOTE:—In the discussion following presentation of this case before the Montreal Neurological Society Feb. 7, 1945, Dr. Wilder Penfield described a patient with a lesion of the temporal lobe who exhibited sexual ideas as a component of his dreamy states. In the cases reported by Dr. Hamill and Dr. Penfield there was no doubt discharge from a higher level of representation, in the jacksonian sense, than that in the present case.

State of Wisconsin General Hospital.

Case Reports

ELECTROENCEPHALOGRAPHIC CHANGES IN A CASE OF SUBARACHNOID HEMORRHAGE

N. Savitsky, M.D.; B. L. Pacella, M.D., and F. D. Stern, M.D., New York

Despite an extensive literature dealing with subarachnoid hemorrhage, we have been unable to find any electroencephalographic studies of this disease. The occurrence of spontaneous bleeding into the subarachnoid space of a patient already in the hospital who had been under observation for a period and had had a previous electroencephalogram afforded an unusual opportunity to follow the electrophysiologic changes which occurred. The electroencephalographic data furnish cogent evidence that significant changes occur within the brain. These data corroborate the clinical and pathologic evidence that such changes do occur within the brain in cases of subarachnoid hemorrhage, even when the source of bleeding is not intracerebral.

REPORT OF CASE

History.—M. H., a man aged 50, was admitted to the Montefiore Hospital on March 4, 1943, with complaints of difficulty in walking, pain in the left arm and a feeling as though "the arm were broken and the cracks were trying to get together." For several years prior to admission he had had moderately severe occipital headaches, which were frequently relieved by acetylsalicylic acid. For two or three years projectile vomiting, usually not preceded by nausea, had at times accompanied these headaches. He had also complained of ready fatigue since the onset of his illness. He had had sharp pains in the arms and, less frequently, in the legs for six years. A few attacks of diplopia had occurred over a period of about five years. There was an unclear history of iritis about two years before admission.

On July 4, 1942 the patient attended a picnic with his wife, where he ate frankfurters. On the way home he felt ill and vomited. The next morning he had chills and complained of dizziness, with objects in the room apparently turning around. His wife noticed that his face was "pulled to the right." This "pulling of the face" gradually became worse over a period of one week. About October 1942 he began to show improvement.

At about this time the patient also noticed weakness of the left side of the body. On July 13 he was admitted to a hospital, where he received physical therapy and intravenous injections of typhoid vaccine, with improvement. During the few months before his admission to the Montefiore Hospital he became worse, and walking became increasingly difficult, until he required support to get about. His wife added that his speech had become less clear. She also described personality changes; he became more abrupt and less courteous.

The past and the family histories were without significance.

Examination.—Physical examination showed no evidence of disease of the internal organs. The blood pressure was 140 systolic and 90 diastolic. The fundi showed arteriosclerotic retinopathy.

Neurologic study revealed shuffling gait, with a tendency to marche à petits pas; weakness of the entire left side of the body; increased deep reflexes, especially of the left side, and a Babinski sign bilaterally, which was more definite on the left side.

Roentgenographic examination of the chest showed slight enlargement of the heart, with a rounded left ventricle and moderate tortuosity and dilatation of the aorta. A roentgenogram of the skull revealed nothing abnormal.

Laboratory Data.—Urine: The reactions for albumin and sugar were negative.

Blood: Determination of the chemical constituents of the blood showed 14.3 mg. of urea nitrogen and 95 mg. of sugar per hundred cubic centimeters of blood. The hemoglobin concentration was 91.8 per cent. The red cells numbered 5,110,000, and the white cells 9.150, with a differential count of 42 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes, 4 per cent eosinophils and 6 per cent mononuclears.

The Wassermann and Kahn reactions were negative.

Spinal Fluid: The fluid was slightly cloudy. The Pandy reaction was 1 plus. The cell count showed 739 crenated cells, 5 fresh red cells and 2 white cells (probably the result of trauma) per cubic millimeter.

The initial pressure was 190 mm. of water; the final pressure, after removal of 10 cc. of fluid, was 120 mm. There was no sign of blood.

The sugar content was 76 mg. and the protein content 16 mg. per hundred cubic centimeters.

Course of Illness.—The patient's condition was relatively stationary until Feb. 3, 1944. On that day he complained of inordinate weakness. During the evening of the same day he began to have projectile vomiting, vertigo, intermittent sensations of coldness and generalized tremulousness. Examination the same day revealed a blood pressure of 220 systolic and 160 diastolic; his pulse was rapid. Except for a bilateral Hoffmann sign, the neurologic signs were unchanged.

During the next few days the patient continued to vomit; he became drowsy and slept a great deal. Rigidity of the neck appeared. The temperature rose slowly, reaching 103.8 F. on February 8, and then receded slowly, becoming normal again on February 15. He improved slowly. Some drowsiness persisted.

On February 8 lumbar puncture yielded a pinkish yellow fluid. The initial pressure was 340 mm of water, and the final pressure, after removal of 10 cc., was 220 mm. The cell count revealed 11,000 red blood cells, with a few crenated forms, and 160 white cells; the total protein content was 69 mg. per hundred cubic centimeters.

On February 10 spinal tap revealed xanthochromic fluid. The Pandy reaction was positive. A cell count showed 273 red blood cells, mostly crenated, 333 polymorphonuclears and 69 lymphocytes. The total protein content was 64 mg per hundred cubic centimeters.

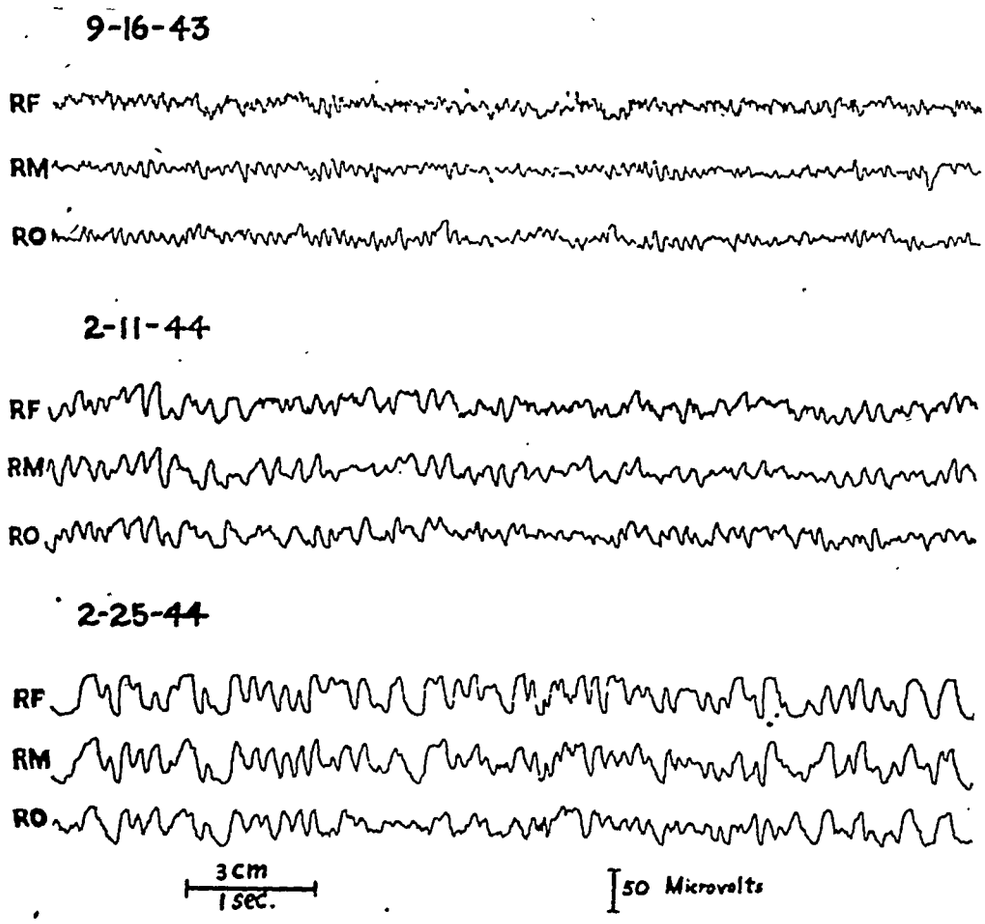
From the Electroencephalographic Laboratory, Montefiore Hospital for Chronic Diseases, Dr. S. P. Goodhart, Director, and the New York State Psychiatric Institute and Hospital, Dr. Nolan D. C. Lewis, Director.

Another spinal tap, on March 16, revealed a clear fluid, a negative Pandy reaction, an initial pressure of 130 mm., and a final pressure, after removal of 10 cc., of 80 mm. per hundred cubic centimeters. The protein content was 52 mg. per hundred cubic centimeters.

Electroencephalographic Observations. — Electroencephalographic tracings were obtained on three separate occasions. The first record was taken Sept. 16, 1943, several months prior to the subarachnoid hemorrhage. This record showed much 7 to 8 cycles per second rhythm over the entire cortex, in addition to random 5 to 6 cycles per second activity. The pattern suggested widespread cerebral disturbance and was consistent with the presence of chronic generalized cerebral changes. No focal abnormalities were evident (figure).

On Feb. 11, 1944, approximately one week after the subarachnoid hemorrhage, an electroencephalogram showed considerably more abnormal activity than was previously recorded, with higher amplitude and a greater incidence of 5 cycles per second serial activity, appearing over the entire brain (figure).

On February 25 another electroencephalogram showed progression in the degree of abnormality, with numerous 2 to 4 per second waves of high amplitude appearing over all regions of the cortex. The last record indicated an increase in intensity of the physiologic disturbance in the brain since the previous electroencephalogram (figure).



Electroencephalograms taken before (Sept. 16, 1943) and after (Feb. 11 and 25, 1944) subarachnoid hemorrhage.

COMMENT

We have found no reports on electroencephalographic studies in cases of subarachnoid hemorrhage in which tracings were made before and after the incident. Although the first record taken prior to the hemorrhage revealed widespread cerebral disturbance, possibly related to chronic degenerative (vascular [?]) changes in the brain, subsequent records revealed a definite increase in this disturbance. The important point in these studies is the observation that the abnormality in the electroencephalogram continued to increase for some time after the hemorrhage in spite of the fact that there were no evidences of increased intracranial pressure or repeated bleeding in the subarachnoid space. This suggests that the observed electrocortical abnormalities are not related solely to the mechanical effect or pressure of the blood on the cortex, but probably are due to other factors in which the cortex is directly affected.

The hypothesis that intracortical changes occur in cases of subarachnoid hemorrhage is in conformity with the previously expressed opinions of several investigators. Bagley,[1] after injecting blood into the subarachnoid and cisternal spaces of dogs, demonstrated the existence of small areas of cortical damage in which the blood had penetrated into the depths of the sulci. Strauss and associates,[2] in his autopsy material, showed that subarachnoid hemorrhage is often accompanied by injury to the cerebral cortex.

1. Bagley, C.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Arch. Neurol. & Psychiat. **17**:18 (July) 1938.

2. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **27**:1080 (May) 1932.

Friedman [3] reported 4 cases in which, in addition to signs of subarachnoid bleeding, evidence of focal lesions of the brain was presented. He stated that the hemiplegia in these cases occurred as a result of seepage of blood into the brain. Noetzel [4] demonstrated that when small amounts of trypan blue are injected into the subarachnoid space, the brain substance becomes colored. He reported 2 cases of old subarachnoid hemorrhage in which there was evidence of diffusion of blood into the brain substance. He noted hemosiderin in the cerebral cortex, the cerebellum and the periphery of the spinal cord. Such continued seepage of blood into and disintegration within the brain may account for the increase in the abnormality of the electroencephalogram.

One of us (*N. S.*) [5] reported sequelae in 8 per cent of his 100 cases of subarachnoid hemorrhage, although in some cases they may have been manifestations of the underlying disease which caused the bleeding into the subarachnoid spaces. Jacksonian attacks occurred in 2 cases; homonymous hemianopsia, in 2 cases; aphasia, in 2 cases; secondary optic nerve atrophy, in 1 case, and a severe memory defect, for a whole year, in 1 case. Mental sequelae in the form of memory defect and Korsakoff psychosis have been described.[6] These mental changes often become severe a few days after the onset, sometimes lasting a few weeks. Carmichael and Stern [7] suggested that the hemolyzed blood acts as a toxic agent, pointing to the latent interval of several weeks between the onset of the subarachnoid hemorrhage and that of the mental syndrome.

SUMMARY

In a case of subarachnoid hemorrhage in which electroencephalographic tracings were made before and, on two separate occasions, subsequent to the hemorrhage, the electroencephalogram revealed diffuse changes after the hemorrhage; the abnormality increased after a time of observation without any associated increased intracranial pressure. This observation suggests that the disturbance is due not merely to the presence of blood on the cortex but to other factors in which the cortex is directly affected, such as seepage into the brain and its disintegration.

1882 Grand Concourse.

722 West One Hundred and Sixty-Eighth Street.

671 West One Hundred and Sixty-Second Street.

3. Friedman, E. D.: Spontaneous Subarachnoid Hemorrhage with Signs of a Focal Lesion in the Brain, J. Mt. Sinai Hosp. **5**:255 (Nov.-Dec.) 1938.

4. Noetzel, H.: Diffusion von Blutfarbstoff in der inneren Randzone und äusseren Oberfläche des Zentralnervensystems bei subarachnoidaler Blutung, Arch. f. Psychiat. **111**:129 (Jan. 10) 1940.

5. Savitsky, N.: Subarachnoid Hemorrhage, in Nelson's Loose Leaf Medicine, New York, Thos. Nelson & Sons, to be published.

6. Tarachow, S.: The Korsakoff Psychosis in Spontaneous Subarachnoid Hemorrhage, Am. J. Psychiat. **95**:887 (Jan.) 1939.

7. Carmichael, E. A., and Stern, R. O.: Korsakoff's Syndrome: Its Histopathology, Brain **54**:189 (June) 1931.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

FUNCTIONAL ORGANIZATION OF THE MEDIAL ASPECT OF THE PRIMATE CORTEX. PERCIVAL BAILEY, GERHARDT VON BONIN, EDWARD W. DAVIS, HUGH H. GAROL, WARREN S. MCCULLOCH, EPHRAIM ROSEMAN and ANIBAL SILVEIRA, J. Neurophysiol. **7**:51 (Jan.) 1944.

Bailey and his collaborators used the strychnine technic to determine the physiologically distinguishable areas on the medial surface of the cerebral cortex in Macaca mulatta and chimpanzees. The authors found area 24, in the anterior portion of the gyrus cinguli, to be a suppressor area. From area 23, in the posterior and superior part, impulses could be traced to the preoccipital and parastriate areas and, in the macaque, to the anterior nucleus of the thalamus. Area 29, in the gyrus cinguli and near the splenium of the corpus callosum, had no other cortical connections but in the macaque projected to the anterior nucleus of the thalamus. Along the sulcus cinguli a region homologous with areas 32 and 31 was found to receive connections from all known suppressor areas of the cortex but did not of itself project to these areas. Commissural connections were demonstrated for area 32, but not for area 31. The firing characteristics were determined in the chimpanzee for areas on the medial surface of the frontal lobe. These areas may correspond with Brodmann's areas 10, 11 and 12. In the macaque these areas could not be identified.

FORSTER, Philadelphia.

STUDIES ON THE TREATMENT OF EPIDEMIC EXPERIMENTAL POLIOMYELITIS WITH POLIOMYELITIS ANTISTREPTOCOCCIC SERUM: SUMMARY OF RESULTS. E. C. ROSENOW, Proc. Staff Meet., Mayo Clin. **18**:403 (Oct. 20) 1943.

Rosenow summarizes the results of his studies, which, he believes, indicate a causal relation of the streptococcus to poliomyelitis, the proof being the production of the classic clinical and pathologic picture of poliomyelitis in monkeys with virus derived from streptococci.

In 1916 Rosenow first immunized horses with freshly isolated strains of the living streptococcus of poliomyelitis which he claims to have obtained from human beings. Later he employed strains freshly isolated from the spinal cords of monkeys which had died of experimental poliomyelitis after inoculation of the virus. At the end of the period of immunization the antistreptococcic horse serum, in extremely high dilutions, agglutinated specifically the poliomyelitis type of streptococcus. It protected rabbits against inoculations with the streptococcus and monkeys against inoculation with poliomyelitis virus.

Immune serum was first employed for patients during the 1917 epidemic. The serum was administered as soon as the diagnosis was established. The mortality rate in an untreated group of 23 patients was 35 per cent. Of the 58 patients who received the serum, 10 (17.2 per cent) died. Aside from the 7 patients who were practically moribund at the time of the first serum treatment and died, 3 (5.9 per cent) of 51 patients died for whom the serum might have been beneficial. Paralysis did not develop in any of the 19 patients to whom serum treatment was given before its onset, and all promptly recovered. Patients who showed evidence of bulbar involvement, and even those in the early stages of partial or complete coma, often responded favorably to administration of the serum, provided it was given soon after the onset of these symptoms.

The current method of preparation of the antiserum is as follows: Freshly isolated dense suspensions of streptococci are placed in glycerin (2 parts) and a 25 per cent solution of sodium chloride (1 part) and kept in a refrigerator. Antigenic specificity is preserved almost indefinitely. All subsequent batches of antistreptococcic serum used for treatment are prepared by diluting such dense suspensions as are needed for injections throughout the period of immunization.

Of the total of 2,664 patients who were treated with the serum, 252 (9.6 per cent) died, as compared with 583 (21.3 per cent) of 2,737 patients in the same epidemic who were not given serum. In experiments with monkeys, the animals who were given serum exhibited a mortality rate one-half to one-third that of the untreated control group.

In the course of these studies, the euglobulin fraction of poliomyelitis antistreptococcic serum was found diagnostic when employed in a cutaneous test. Ninety-two per cent of 324 persons ill with poliomyelitis for from one to fifteen days showed an erythematous patch of 5 sq. cm. or more in from five to ten minutes after the intradermal injection of the euglobulin fraction.

Rosenow states that objections to the general adoption of this treatment have been removed since his recent demonstration of microdiplococci in filtrates of the virus. Further, the classic picture of the disease has been produced in monkeys with virus derived from the streptococcus, and the diagnostic and preventive action of the serum has been demonstrated.

GUTTMAN, New York.

ON THE MODE OF REPRESENTATION OF MOVEMENTS IN THE MOTOR CORTEX, WITH SPECIAL REFERENCE TO "CONVULSIONS BEGINNING UNILATERALLY" (JACKSON). F. M. R. WALSHE, Brain **66**:104, 1943.

Walshe points out that the first indication of a representation of movement and of function in the cerebral cortex was deduced from clinical observation. The clinical neurologist today, viewing the knowledge at hand regarding the nature of the cortical representation of movements, finds two apparently unrelated sources of information: (1) the literature of electrical stimulation of the cortex, presenting the picture of a mosaic of excitable points, each yielding a characteristic motor response, as well as the instability of the

excitable cortex, as evidenced by facilitation, deviation and reversal; and (2) the clinical phenomena of jacksonian fits, with their three predominant foci in the motor cortex, resulting in movements of the thumb and index finger, the angle of the mouth and the hallux. The literature on experimental physiology of the motor cortex has been primarily oriented along anatomic lines; that is, it has been more concerned with the "where" than the "how" of the cortical representation of movement. Jackson pointed out that the cerebral cortex represents sensorimotor processes, and not the performing parts. That muscles themselves are not represented in the cortex is indicated by the common clinical experience of paralysis of the extensors of the wrist in voluntary extension, with the presence of powerful synergistic contraction in forced grasping. Through study of the movements elicited by electrical excitation or disease processes of the cortex, the nervous mechanisms involved in a given movement have been determined, and so the movement has come to be considered localized, or represented. Building up on this basis produced general principles of cortical representation and of the mode in which the cortex initiates movement. Thus used, "representation" means all those processes in the cortex by which these visible results are brought about. However, according to Jackson's hypothesis, the motor cortex represents all the movements which an individual organism is capable of initiating. Thus, a pattern of excitation must exist for each purposive movement, and the leading motile parts must have the most extensive representation; the greater the spatial extension of representing cortical structures, the more complete must be the integration. The motor cortex must be considered not as a mosaic of abrupt localizations but as a complex pattern of overlapping and graded representations. Therefore, after a focal lesion, while the functions of the destroyed area are not taken over by other areas, the vast repertory of movement left may allow the functional deficit to be hidden; on the contrary, a stimulating lesion may release a widespread convulsion without necessarily a wide distribution of the excitatory process through the cortex. Walshe points out the difficulty in reconciling the theories of punctate localization with the phenomena of facilitation, deviation and reversal of response, but on the basis of Jackson's hypothesis of cortical representation, these phenomena are accounted for by the changes in the relative thresholds of excitability in the different patterns of excitation. Each focus in the motor cortex has through neuronal connections the substratum of many patterns of excitation, but one of these is primary. Appropriate antecedent local stimulation will bring about facilitation by lowering the threshold of excitability, so that the change is not spatial, but is due to deviation of response. Therefore deviation, as well as augmentation and reversal, of response, is a consequence of facilitation. Coordination in time, resulting in the orderly sequence of movement, probably has as its primary factor facilitation. A destroying lesion of the cortex, in both man and experimental animals, is followed by partial return of function. This, Walshe contends, is inexplicable on the basis of the theory of punctate localization but is consistent with Jackson's hypothesis; in other words, moving parts must have wide representation in the cortex, and cortical points must contain many representations. Walshe reviews the clinical features involved in convulsions beginning unilaterally and indicates those which tend to corroborate Jackson's hypothesis of representation and the foregoing correlation of that hypothesis with present neurophysiologic observations. Since a convulsion may spread although cortical discharge may remain restricted, and since the patterns of unilateral seizures beginning in two different peripheral parts differ, Walshe concludes that the field of convulsion in the musculature is probably always wider than the field of cortical excitation. The compound order of spread of a unilateral seizure (increase in intensity as well as in distribution) is explicable on Jackson's hypothesis, but not on the theory of punctate localization. The onset of jacksonian seizures in one of three areas is not explicable on the basis of the punctate theory but can be accounted for only by Jackson's hypothesis, and these three "leading parts" probably have the widest fields of low threshold excitability. The spread of unilateral seizures is not always consistent with the topographic charts of the motor cortex; these exceptions are consistent with the jacksonian concept of representation. Jackson maintained that movements of both halves of the body were represented in the motor cortex of each hemisphere, and so focal convulsions from one motor cortex could become generalized. Walshe compares this with the frequent observation of bilateral neurologic signs in cases of severe hemiplegia. Focal seizures characterized by sudden transient motor impairment or loss of speech may afford confirmation of the presence of inhibitory areas of the cortex. The same mechanism may explain the postseizure flaccid coma.

FORSTER, Philadelphia.

Psychiatry and Psychopathology

A NEUROPSYCHIATRIC VIEW OF GERMAN CULTURE. RICHARD M. BRICKNER and L. VOSBURGH LYONS, J. Nerv. & Ment. Dis. **98**:281 (Sept.) 1943.

Brickner and Lyons point out that the technics of neurology, psychiatry, psychology and anthropology have had little acceptance thus far in the solution of group problems, the oversimplifications of economics and politics still holding sway. Knowledge of group behaviors gained through use of these sciences are applied to the problem of the German cultural pattern.

There has existed for more than one hundred years a dominant German cultural attitude, characterized by systematized megalomania, sense of mission, suspiciousness, sense of persecution, retrospective falsification, projection, mysticism, lack of critical judgment, lack of humor, extreme use of rationalization and impeccably logical elaboration of original premises. This constellation of paranoid thinking is a dominant trait in German culture and is considered to be not only acceptable but desirable. It is dangerous to the rest of the world because it is contagious, murderous and enslaving and attempts to be dominating.

The outlook with regard to treatment is not as dismal at it would be with the paranoid individual, since paranoid and nonparanoid elements are embodied in separate persons, rather than in the same personality. The hope in the therapeutic program depends on that segment of the population which is nonconforming to the dominant cultural attitude. The first step in treatment would be the immediate identification of conformers and nonconformers, with the disposal of the former so as to prevent their having any kind of power or influence. This would mean putting to death the conformist leaders

and isolation and supervision of the large body remaining. An essential step in the program of long term treatment would be the establishment of the nonconforming segment of the population in power and political influence. Reculturization, the replacement of old ways of thinking and old institutions by new ones, and a general atmosphere of freedom from paranoid values are therapeutic measures of importance. In education the aim would be to substitute Germans who could think objectively and rationally about Germany or any other subject for those of the older education, who were taught primarily the glorification of Germany. This principle and aim should permeate and guide the teaching of all the subjects of the curriculum, especially history, geography and anthropology. Adult education of a similar nature, through the agencies of press, screen, radio, stage, meetings and the children, would be equally important. The elimination of the old pattern of domestic hierarchy under the harsh and dominant father would be one of the aims of the educative process. The small army left remaining would have to be totally reorganized to put an end to the Prussian system of military caste and prestige. The same need would apply to the police force.

The authors recognize that the aforeoutlined measures could be applied only in the framework of new political and economic organization, but they feel that the latter would be futile without the employment of plans of the type they describe.

CHODOFF, Langley Field, Va.

PROLONGED CASE OF GRIEF REACTION TREATED BY ELECTRIC SHOCK. ABRAHAM MYERSON, New England J. Med. **230**:255 (March 2) 1944.

Myerson reports on 4 female patients suffering from "grief reaction" after the death of a husband or child. The symptoms were severe and prolonged, and psychotherapy was tried, without success. One patient had had a depression four years, and it was necessary to produce amentia by electric shock before further shock treatment could effect abatement of symptoms and return of memory. The other 3 patients, whose loss by death was recent, responded after a few electric shock treatments and achieved adequate reorganization of personality.

Myerson concludes that "physiologic alterations of an unknown type take place, and this is the basis of recovery."

GUTTMAN, Philadelphia.

TYPES OF FEMALE CASTRATION REACTION. EMELINE P. HAYWARD, Psychoanalyt. Quart. **13**:45, 1944.

Women who have oriented their lives around penis envy fall into two main groups—the wish fulfilment type and the revengeful type. The revengeful type lives a barren existence, all her potentialities being directed toward revenging herself on the world for her defect. The wish fulfilment type has acquired a penis equivalent, which frees her to use her intellectual potentialities in a constructive manner. Hayward suggests that the little girl who falls prey to penis envy in the anal-sadistic stage is the one who develops into the revengeful type of woman. This situation is frequently encountered when a little girl has been raised with a brother who is nearly her own age. The girl who develops into the wish fulfilment type of woman becomes preoccupied with penis envy after she has reached the phallic level. Such a woman has had no brothers close to her own age.

PEARSON, Philadelphia.

Diseases of the Brain

ELECTROENCEPHALOGRAPHY IN CHRONIC POST-TRAUMATIC SYNDROMES. MOLLIE E. HEPPENSTALL and DENIS HILL, Lancet **1**:261 (Feb. 27) 1943.

Heppenstall and Hill report 150 cases of post-traumatic syndromes studied by means of electroencephalography. A three channel Grass ink-writing oscillograph was used. The results are tabulated as follows:

Diagnosis	Total Number of Cases	Abnormal Tracings		Abnormal Electroencephalograms		
		No.	%	Diffuse	Focal	With Hyperventilation Only
Postconcussive syndrome	58	33	57	16	16	1
Post-traumatic epilepsy	29	22	76	9	13	0
Anxiety state	21	10	48	7	1	2
Depressive state	19	8	42	5	2	1
Schizophrenic state	2	0	..	0	0	0
Hysteria	14	3	21	2	0	1
Psychopathy	7	2	29	2	0	0
Organic states	87	55	63	25	29	1
Functional states	63	23	37	16	3	4

The time elapsing since the injury seems to bear no relation to the type of electroencephalogram, but the age at which the injury occurred is important. When the injury occurred before the age of 20 years, 65 per cent of the tracings were abnormal; when it occurred in a patient over 20 years of age, 46 per cent were abnormal. The response to hyperventilation showed abnormalities in 39 per cent of cases in the 20 year group and in 16 per cent of cases in the group over 20 years of age. The period of post-traumatic amnesia was of some significance. When it was less than one hour, 43 per cent of the tracings were abnormal; when it was less than one day, 52 per cent were abnormal, and when it was more than one day, 58 per cent were abnormal. These results are of more significance when the abnormalities are divided into diffuse and focal changes. Of the focal abnormalities, 13 per cent occurred in the first group, 48 per cent in the second group and 55 per cent in the third group.

In 18 of the cases of organic disorders the personal history was abnormal, as compared with 33 cases of the constitutional and reactive states. Of the cases in which the personal history was abnormal, abnormal electroencephalograms were present in 37 per cent, and of the cases in which the personal history was normal, abnormal tracings were obtained in 60 per cent. Focal abnormal records were present in 33 per cent of the cases in which the personal history was abnormal and in 47 per cent of the cases in which the personal history was normal. Of the cases in which a family history of neurosis was obtained, focal abnormalities appeared in 26 per cent and diffuse abnormalities in 74 per cent, and of cases in which the family history was normal, focal abnormalities appeared in 54 per cent and diffuse abnormalities in 46 per cent. The assessment of abnormal family histories was wide and was based on the presence of epilepsy, psychosis, severe neurosis, mental defect and psychopathic personality.

The author maintains that abnormal personal and family histories are not likely to increase the probability of an abnormal electroencephalographic record; but when the electroencephalogram is abnormal, the focal changes are more frequent in cases in which the per-

sonal history is normal and diffuse changes in cases in which the personal history is abnormal. Therefore, diffuse abnormalities in the electroencephalogram in a case of a post-traumatic state do not necessarily indicate the presence of cerebral damage.

SANDERS, Philadelphia.

Peripheral and Cranial Nerves

PIGMENTARY DEGENERATION OF RETINA AND NERVE TYPE OF DEAFNESS. W. A. SIRLES and H. SLAUGHTER, Am. J. Ophth. **26**:961 (Sept.) 1943.

Sirles and Slaughter report 12 cases of retinitis pigmentosa. The patients were examined both subjectively and objectively and were considered to have typical cases of this disease. A careful otolaryngologic history was obtained, and thorough examinations were made, including audiometric tests, of all patients. Of the 12 patients, 6 were deaf, as indicated by the audiograms, and showed the typical nerve type of deafness. Only 4 of these gave a history of impairment of hearing. Three of the 4 patients who gave a history of deafness had noticed this symptom from two to twenty-eight years before they experienced any ocular symptoms. It is suggested that a common defect of the germ plasm is present in the anlage of the inner ear and the retina.

J. A. M. A.

NERVE TRANSPLANTATION. N. I. PROPPER-GRASHCHENKOV, Am. Rev. Soviet Med. **1**:28 (Oct.) 1943.

Propper-Grashchenkov discusses experiments on replacement of defects in peripheral nerves, in particular, the Ignatov method of utilizing human nerves taken from corpses and treated with solution of formaldehyde. Ignatov used corresponding nerves, so that the diameters of the nerves could be matched. During the Finnish war there were 13 cases of transplantation in which the defects were so large that direct contact of the severed nerves was impossible. In 1 case a defect of the sciatic nerve amounted to 12 cm. There were cases of defects of the median, radial and ulnar nerves. Repeated chronaxia examinations were made, and motor and sensory functions of the involved extremities were tested with electrometric instruments. Observations demonstrated that the implanted nerve acted as a dead tissue bridge, thereby assuring the regeneration of the nerve fibers. Usually, when motor and sensory functions are lost, a disturbance takes place in the circulation and perspiration of the extremity. It becomes cyanotic, clammy and often covered with ulcers. Every case of transplantation of the formaldehyde-treated nerve tissue showed improvement in each of these dystrophic processes. The transplantation of human nerves in large peripheral nerve defects accelerates the regeneration and reestablishment of the lost motor, sensory and trophic functions and prevents the wounded from becoming invalids.

J. A. M. A.

ATTEMPTS TO ISOLATE POLIOMYELITIS VIRUS FROM URINE. J. A. TOOMEY, L. A. TISCHER and W. S. TAKACS, J. Pediat. **23**:172 (Aug.) 1943.

Toomey and his collaborators tried to demonstrate the virus of poliomyelitis in the urine of patients with paralysis of the bladder. Their attempt was a failure when the monkey was used as the test animal, even though such specimens were obtained at an optimal time, that is, coincident with the onset of the paralysis. Urine obtained post mortem from the bladders of patients with poliomyelitis was tested for the presence of the virus on eastern cotton rats. These tests also gave negative results.

J. A. M. A.

HERPES ZOSTER OPHTHALMICUS: TWO RARE MANIFESTATIONS. T. G. W. PARRY and G. C. LASZLO, Brit. J. Ophth. **27**:465 (Oct.) 1943.

Parry and Laszlo direct attention to various ophthalmic conditions caused by herpes zoster. A woman aged 52 had had an attack of herpes zoster along the ophthalmic branch of the right fifth nerve six weeks previously. The cornea was not involved, but there was a cutaneous eruption with severe pain. Three and a half weeks after the eruption the patient suddenly lost sight in her right eye. The disorder was diagnosed as acute retrobulbar neuritis. After five weeks the visual acuity of the patient had improved. A man aged 33 had had "shingles" on his chest. Three weeks later he felt giddy and had double vision. Examination revealed paresis of the right abducens nerve. The condition gradually cleared up. The few existing statistics on the late ophthalmic involvements in cases of herpes zoster reveal that they occur in the following order of frequency: iridocyclitis (usually a complication of keratitis), optic neuritis and paralysis of the third, fourth and sixth cranial nerves. Retrobulbar neuritis has not previously been mentioned as a signal of herpes zoster.

J. A. M. A.

LOCALISED NEURITIS OF THE SHOULDER GIRDLE. J. D. SPILLANE, Lancet **2**:532 (Oct. 30) 1943.

Spillane describes 46 cases of localized neuritis of the shoulder girdle, which he divides into two groups: in one, of 26 cases, the disturbance developed while the patients were in the hospital or a convalescent home. All these were recovering from an illness (dysentery, malaria, gunshot wound, local sepsis, typhoid, infective hepatitis, a tuberculous lymph gland of the neck, pharyngitis, lobar pneumonia and cerebrospinal meningitis). In the other 20 cases the men were ill while on duty in the field. In 42 cases the first symptom was sharp pain about the shoulder at localized points. The pain was usually worse at night. In all but 1 case there was no fever. There was no rigidity of the neck or back and no diffuse hyperesthesia, and only in the cases in which the deltoid was affected were there sensory changes. The painful sites were tender, but there were no vasomotor changes. Atrophy was well localized and usually pronounced, often led to much disability and affected chiefly the spinatus, the deltoid, the serratus magnus and the trapezius muscles. The patients were treated with analgesics and physical therapy and rest; but there was little alteration in the course of the illness, and atrophy and weakness persisted in the affected muscles in several patients for seven or eight months.

The illness was distinguished from poliomyelitis by absence of changes in the spinal fluid, by the distribution of the paralysis (peripheral rather than segmental) and by absence of general signs of infection or of diffuse hyperesthesia. The condition was thought not to be brachial neuritis or radiculitis because isolated muscles were involved. In these disorders fibrillation and alteration of reflexes are common, and recovery is the rule.

The cause could not be determined. Patients with a history of direct trauma were not included in the series. Repeated slight trauma, such as carrying a pack or rifle could not be excluded in many cases, but in many

other cases the patients were sedentary in their daily duties.

McCarter, Philadelphia.

Costoclavicular Compression of the Subclavian Artery and Vein: Relation to the Scalenus Anticus Syndrome. M. A. Falconer and G. Weddell, Lancet **2**:539 (Oct. 30) 1943.

Falconer and Weddell found the subclavian vessels to be compressed by the clavicle and the first rib alone in 2 patients, without effect from the scalenus anticus muscle, to a sufficient degree to produce paresthesias in both patients and weakness and vasomotor changes in 1 of them. Pressure by the scalenus anticus muscle on a rudimentary cervical rib, as well as costoclavicular compression, caused similar trouble in a third patient; in another, weakness and wasting alone, with no vascular signs, were produced by a fibrous band extending from a long transverse process of the seventh cervical vertebra to a point on the first rib between the course of the first thoracic nerve root and the subclavian artery.

As an aid in diagnosis the authors used two test maneuvers: hyperextension of the neck and downward and backward bracing of the shoulders, the latter being found more effective. The role of the scalenus muscle was tested by paralyzing it with procaine; later it was cut if the condition was severe enough to warrant operation.

Of 50 "normal" men and 50 "normal" women, several showed evidence of the scalenus anticus syndrome when the test maneuvers were carried out. The authors point out that symptoms arise only when this compression can be evoked with ease. In some instances this may mean that the patient has cold blue hands, with a tendency to chilblains, and others, perhaps actual thromboses or even gangrene.

Patients with mild symptoms were relieved by postural exercises; 1 of the authors' patients ceased to complain after his heavy basic training, with pack carrying, was over. Severe conditions merit surgical exploration. The scalenus anticus muscle may then be carefully stimulated to determine its role in the production of symptoms. If this fails to cause symptoms, the finger may be slipped between the artery and underlying rib and the clavicle above to see whether bracing the shoulders will pinch it. Actual compression of the vessels may thus be seen. If this exists, the authors recommend resection of a small segment of rib beneath the artery to relieve pressure symptoms.

McCarter, Philadelphia.

Treatment, Neurosurgery

Sodium Amytal Narcosis in Treatment of Operational Fatigue in Combat Aircrews. Donald W. Hastings, Bernard C. Glueck and David G. Wright, War Med. **5**:368 (June) 1944.

Operational fatigue is a syndrome composed of emotional illness and fatigue, which occurred in a certain percentage of fundamentally stable combat personnel, usually after twelve to eighteen heavy bombardment missions, which exposed the participants to harrowing experiences, tension, fatigue and lack of sleep.

The patients look pale and fatigued. They are irritable and self accusatory about their irritability. They have difficulty in going to sleep; and when they do, they suffer from vivid and terrifying battle nightmares. They are depressed and retarded and suffer from severe anxiety, tremors and gastric and cardiovascular symptoms.

Because depression played a prominent part in the symptoms, it was thought that modified sodium amytal narcosis might be of benefit, since it was useful in the treatment of manic-depressive psychosis. The period of the narcosis was arbitrarily limited to ninety-six hours, followed by a week of convalescence and then return to full duty.

Follow-up studies two months after narcosis therapy were made on 69 patients. Seventy per cent were performing adequately on full duty, and 25 per cent, on ground duty; 5 per cent still had persistent anxiety symptoms.

Pearson, Philadelphia.

Encephalography, Ventriculography, Roentgenography

Osteomyelitis of the Frontal Bone. Lester A. Brown, Arch. Otolaryng. **39**:485 (June) 1944.

Osteomyelitis of the frontal bone is secondary to acute frontal sinusitis in the majority of cases. Only rarely is the condition secondary to chronic frontal sinusitis because during the course of the infection the frontal bone tends to form its own barrier to the spread of the infection. Occasionally, compound fracture of the plates of the frontal sinus or of the bone beyond the confines of the sinus may lead to osteomyelitis. Another possible cause is infection resulting from operation for acute sinusitis when the external approach is employed. The most common symptom is headache. This may vary in intensity from mild discomfort to excruciating pain. Usually the headache is frontal, but occasionally it may be occipital. High fever is not common. The most suggestive finding on examination is a doughy subperiosteal swelling on one or on both sides of the forehead, extending from the brow toward the hair line. The height of the swelling is usually proportional to the osseous involvement. There is tenderness over the involved sinus and sometimes over the entire forehead. Roentgenographic examination reveals decalcification in the involved area.

Brown reports a series of 10 cases of osteomyelitis of the frontal bone, proved at operation, in which most of the usual complications of the disease occurred. These included, in their order of frequency: epidural abscess, cerebral abscess, meningitis, subdural abscess and subperiosteal abscess. Subdural abscess occurred in 2 cases and was rapidly fatal in both, death apparently being due to medullary compression resulting from rapidly rising intracranial pressure. In all the other cases recovery occurred.

Once the diagnosis of osteomyelitis has been made, treatment resolves itself into (1) the attempt to remove the area of infected bone with an area of good bone around it, (2) the attempt to prevent the spread of the osteomyelitis to the supposedly uninfected bone and (3) the treatment of complications.

Ryan, Medical Corps,
Army of the United States.

Society Transactions

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

CLARENCE P. OBERNDORF, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, March 14, 1944

Biochemical and Electroencephalographic Changes Associated with Delirium Tremens. DR. MARGARET A. KENNARD, DR. ERNST BUEDING and DR. S. BERNARD WORTIS.

In a preliminary study certain of the changes underlying the symptoms of delirium tremens were investigated. This was done by means of biochemical analysis and electroencephalographic studies of a series of 49 alcoholic patients, 40 of whom had symptoms characteristic of acute delirium tremens. The remaining 9 patients, without delirium tremens, were used as controls.

Biochemical Investigations.—Zuckerkandl (Ueber das Verhältnis der Natrium- zur Chlorausscheidung im Harn: Der Natrium-Chlor-Quotient, *Klin. Wchnschr.* **14**:567, 1935) demonstrated that normal human subjects excrete equivalent amounts of sodium and chloride in the urine. The ratio of chloride to sodium in terms of equivalent weights of these two ions varied from 0.9 to 1.15; in other words, normally the same amounts of sodium and chloride are excreted. In pathologic conditions associated with inflammation of the serous membranes, such as pleurisy, ascites or polyarthritis, Siedek and Zuckerkandl (Ueber das Verhältnis der Natrium-zur Chlorausscheidung im Harn: Der NaCl-Quotient der entzündlichen und kardialen Erkrankungen, *Klin. Wchnschr.* **14**:1137, 1935) reported that there was retention of sodium and that, as a consequence, much less sodium than chloride was excreted in the urine.

Since delirium tremens is associated with a considerable loss of water and salt, the excretion of sodium and chloride in the urine was investigated. Of 19 patients studied so far, 11 showed a chloride-sodium ratio outside the control range of 0.8 to 1.2 on admission. Seven of these 11 patients excreted less chloride than its equivalent of sodium, and for 4 patients the reverse was true. For the 7 patients with low chloride excretion on admission the chloride-sodium ratio returned to normal in one to four days.

The abnormalities in this ratio were often more pronounced for the urine excreted during the four hours after 1.5 liters of water had been given the patient. The return to normal of the chloride-sodium ratio was not preceded by a reversal of this ratio; in other words, there was not an excess of chloride over sodium. This indicates that no retention of chloride or excessive excretion of sodium had existed at the time of admission of these patients. It is more likely that an excessive loss of chloride occurred at this time.

Electroencephalographic Study. — Twenty-three patients with delirium tremens showed a pronounced tendency in all records to wave forms of low amplitude and fast, 20 per second activity. There was in all records a relatively low percentage of 8 to 12 per second activity. The patients who showed least of this alpha activity, of medium rate and low amplitude, were persons whose history and occupation indicated deterioration, although their symptoms in the acute attack were no more severe than the symptoms of patients with more nearly normal patterns of cerebral activity.

It was also found that the patients who had the highest percentage of alpha activity on admission were those who recovered most rapidly. For all patients with clinical recovery there was an increase in the percentage of alpha activity in the record. But this increase was less pronounced in the records of the "deteriorated" patients which showed originally the greatest deviation from the normal pattern.

Phlebothrombosis and Phlebostasis of the Brain in the Newborn and in Early Childhood. DR. OTTO MARBURG and DR. LOUIS CASAMAJOR.

This paper was published in full in a previous issue of the ARCHIVES (**52**:170 [Sept.] 1944).

DISCUSSION

DR. TRACY J. PUTNAM: Dr. Marburg deserves to be commended for avoiding the error which is all too common in neuropathology of leaping abruptly from the clinical picture or the gross pathologic changes to the ultimate etiologic factors. It is seldom one can make this leap. One must usually move step by step from what is observed at autopsy to the point where the chain of evidence begins for practical purposes. It is gratifying that Dr. Marburg has analyzed these lesions in terms of damage to or disturbance of the venous drainage, for another shortcoming of classic neurology is its neglect of the venous system. The pathologist studying Weigert preparations is apt to regard the vascular system as being merely ancillary to the nerve structures, when actually it is the other way around —the nerve structures are entirely dependent on their circulation. Moreover, while the term "vascular injury" is extremely common in neuropathology, and the general outlines of the results of disturbances in the vascular supply have been familiar since the days of Wepfer, vascular injury practically always means arterial thrombosis. This was well shown by Hassin, for example, in his discussion on the possible vascular origin of the lesions of multiple sclerosis. He said such lesions had nothing to do with the disposition of the arteries of the nervous system and dismissed the whole matter, as others have done.

The lesions which Dr. Marburg presented have been well described before. It has not been clearly recognized that such lesions, and others of this type, are within reasonable limits to be interpreted as the result of disturbance in the venous circulation. It is not difficult to see how this error came about. First, the classic neuropathologic stains successfully concealed the vascular system. That is what they were for. They were intended to stain the nerve elements, and usually not the mesodermal elements, and they were apt to

conceal the content of the blood vessels. Second, the damage takes place rapidly, without any question. Once a thrombus or any other type of obstruction forms in a vein the damage to the parenchyma takes place in a few hours. It is there to stay; the actual nerve elements never regenerate, and the subsequent events consist in the formation of a scar. By the time the scar is well formed the thrombi may have disappeared entirely; so it is fortunate that Professor Marburg encountered the telltale thrombi in the proper place in some of the lesions. I take it that some of the lesions he studied had already passed the stage at which thrombi could be seen. In any city under bombardment there are always more burns and ruins than there are fires in progress, but one usually concludes from the ruin that there has been a fire; so with these lesions, one must study a series before concluding that the scar must have resulted from this type of injury, and not from any other. From the injury, one can then pass to the next step in the progress of the formation of the lesion. As to whether or not the injury is always trauma in cases of this kind I am not wholly convinced. I believe I have seen a case much like Dr. Casamajor's second case in which the lesion was already in the scarred stage within a week after birth. The acute process must therefore have occurred before birth. This may have been one of the cases which Professor Marburg mentioned in which the lesions occurred as the result of injury during fetal life. I think this study represents an important addition to the series of pathologic pictures which begins with the birth injuries and passes through diffuse sclerosis and so into multiple sclerosis and the encephalitides; all these processes may or may not be due to the so-called inflammatory phenomena, which are seen about as often in cases in which the origin was obviously traumatic as in cases in which infection may conceivably have played a part.

Professor Marburg has performed a great service in again calling to attention the extraordinary prevalence of birth injuries, a subject the gravity of which is well recognized by obstetricians, neurologists and psychiatrists. The unfortunate victims are usually swept out of the broader currents of daily life and collect in the backwaters of institutions, and so are less often seen. It is important, however, to remind oneself of their existence and to keep struggling with the problem of how such cases may be prevented. It is clear that such conditions as have been presented tonight can scarcely be cured and that surgical intervention would not in the least be helpful to any patient of this group. Whether chemical or biologic means may be found to prevent such lesions is an important study for the future. I wish to compliment the authors for pointing out the cardinal features of this syndrome and its human and economic importance.

DR. JOSEPH H. GLOBUS: I am glad Dr. Marburg reopened the question of porencephaly. Indeed, he did not use the term "porencephaly," but the designation can well be used to describe the pathologic picture in the cases presented tonight. The brain showed numerous extremely large cavities, in accordance with the classification of porencephaly.

I hoped that Dr. Marburg would recall a case which I presented about twenty-two years ago in which the dissolution of brain tissue which led to the cavity formation was due to interference with the blood supply. At that time it was my opinion that the interference with the blood supply was the result of strangulation of the blood vessels by thickened meninges in the region of their penetration into the cerebral cortex. I was able to demonstrate the presence of actual scar tissue at this point. The vessels in their course were collapsed and empty. In this way, I thought, I have shown that the dissolution of brain tissue is the result of interference with the blood supply, and this, in turn, is the result of strangulation of blood vessels.

Dr. Marburg has given important support to my concept by demonstrating that the interference with the venous supply was responsible for the pathologic process in his cases.

DR. OTTO MARBURG: In reply to Dr. Globus' comment on porencephaly, we did not use this term in our case because porencephaly means the presence of cavities in the brain substance communicating with the lateral ventricles. There must be an open connection between the cavities and the ventricles.

DR. LOUIS CASAMAJOR: I am afraid Dr. Putnam misunderstood what I said. The second patient did not show the condition immediately after birth. The child was apparently normal at birth, and the obstetrician told the parents that the baby was normal; he seemed normal, except that they were unable to find any satisfactory formula. Nothing abnormal was noted until two and a half months after birth, when the left foot became spastic. The opisthotonos did not appear until four or five months after birth, and from then on the retraction of the head increased until it reached the position seen in the illustrations. I had difficulty in thinking of this condition as congenital, and until Dr. Marburg went over the sections and offered me this theory of phlebothrombosis, I was at a loss to understand why the condition was progressive. The child was 1 year old before I saw him. I knew nothing about the case before that except for the history, which was that of a progressive condition.

DR. H. A. RILEY: Is it Dr. Casamajor's belief that this child had a normal brain when it was born and that the situation seen at autopsy developed after birth?

DR. LOUIS CASAMAJOR: I do not know. The child was said to be normal; I believe that when he was born he did not have the kind of a brain he had when he died. The brain may not have been normal at birth, but I believe it was not as degenerated as it was at death. If it had been, I cannot see why the child was 4 or 5 months old before retraction of his head became apparent, after which the opisthotonos progressed until the vertebral column was a hoop. I believe this was a progressive condition, and not congenital at all.

Prognostic Significance of Certain Factors in Schizophrenia. DR. NOLAN D. C. LEWIS.

The modern psychology of schizophrenia has been constructed on the basis of concepts of Kraepelin, Bleuler, Freud, Jung and their immediate derivatives or schools of thought. Kraepelin's work is well known, as is that of Bleuler, who approached the problem from the standpoint of an organically determined change in the associations. His main contribution lies in the painstaking evidence he compiled on the psychologic determination of the majority of schizophrenic manifestations. Jung, studying the problems from his psychologic point of view, concluded that the psychic symptoms were not dependent primarily on disturbances in association. For example, he interpreted schizophrenic negativism as an attitude of rejection, and not as a consequence of interruption in associative processes. Freud's theory of schizophrenia rests basically on the concept of regression from object relations to the state designated as "narcissism."

A better understanding of schizophrenic psychology may be revealed by more complete studies of patients treated with insulin or convulsive shock methods. There is no known pathogenesis of schizophrenia as an entity. Therefore one must consider each subtype separately, an approach which is reenforced by Birnbaum's structure analyses, Kretschmer's multidimensional diagnostics, Bleuler's *Tiefenpsychologie* and other systems of analysis.

There are many blunders in the diagnosis of the schizophrenias, and a better understanding may be effected by carefully organized studies of the outcome.

The pathogenesis and diagnosis of schizophrenia are actively disputed factors, a fact which renders prognosis difficult.

The great diversity in the symptoms, as seen and described in psychiatric clinics and assembled under the diagnosis of schizophrenia, is difficult to explain unless a large number of contributing factors and combinations is assumed.

There is evidence of a central type of schizophrenia, with other, marginal, forms, which may be termed "symptomatic" schizophrenia, and certain acute exogenously determined psychoses. However, one must have proof of the relation of exogenous injury, infections, prepsychotic personality traits and hereditary components before utilizing etiologic factors as a basis for prognosis. Clinically it is advantageous to separate atypical schizophrenic conditions from the main forms and give them an identifying description.

Although it is not the purpose of this paper to discuss shock therapy in any detail, in the present era, which might be designated as one of shock methods, its relation to prognosis should be one of the first considerations. The discordance in the opinions of recognized experts in the field, based chiefly on inadequate, or at least dissimilar, research procedures, has left me, and probably others, without any answer to the following questions: Does shock therapy cure patients otherwise incurable, or only shorten the duration of a schizophrenic illness bearing a favorable prognosis? Is shock therapy the deciding factor in the recovery of patients for whom the prognosis is doubtful? How lasting are the results? Are they more or less permanent than spontaneous or psychotherapeutic recovery? Does shock therapy harm the patient? All patients? Or only certain types of patients?

Kretschmer emphasized that the weak leptosome, with asthenic body build, is highly predisposed to the schizophrenic process and that the pyknic body form is in some way antagonistic to this type of mental disorder. Manz found that catatonic features are more frequent in persons of athletic build and that they tend to favorable remissions. Hebephrenic forms are more frequent in persons of dysplastic habitus. Here there is a tendency to primitive reactions and naïve spontaneous expressions of emotion as dominant features in the prepsychotic character, with exaggerations of these features in the full blown psychosis. For the majority of persons of this type the prognosis is poor, as it is for persons of another special group, with asthenic body build. These patients are highly educated, prepsychotically introverted, hyperesthetic persons—teachers, students of religions and of philosophy, often with interests in reform, who progress rather rapidly to deterioration.

Schizophreniform or atypical schizophrenic attacks in imbeciles are recoverable. There is a question whether such persons are really schizophrenic. When a "nuclear" schizophrenia appears in a feebleminded person, early deterioration may be expected. However, in many persons of a low order of intelligence there develop schizophreniform reactions which have a good prognosis, and, as mentioned before, these reactions probably belong in a separate pattern category.

While isolation of symptoms from a pattern for special consideration is always controversial, certain combinations are of prognostic importance in this respect.

Kraepelin, Stransky, Meyer and many, more recent, investigators have observed that the acute occurrence of catatonic forms carries a favorable prognosis, but Bleuler found that schizophrenias in which the catatonic features appeared gradually had an unfavorable prognosis. Kraepelin pointed out that the condition of deep stupor and of severe catatonic excitement had a favorable outcome; however, semistuporous states with continued stereotypy in the quiet periods have a bad significance. It is the experience of most psychiatrists that the majority of patients who have passed through a severe catatonic psychosis will carry the marks of it through life, even though they are independent and socially adjusted.

Some paranoid ideas can be regarded as temporary compensatory symptoms, and therefore not "nuclear." Ideas of persecution and poisoning in a moderate degree have little unfavorable significance. In fact, some self-reference tendencies and vague symptoms of splitting tend toward a cure, or a cure with a remaining defect. However, it is realized that massive paranoid developments are fixed and resistant to therapy.

It is important to know, for diagnostic and prognostic reasons, as much as possible about the following features of a given case:

1. The influence of prepsychotic factors
   - (*a*) Heredity
   - (*b*) Morphologic type
   - (*c*) Prepsychotic character
   - (*d*) Social factors
   - (*e*) Intellectual foundations
   - (*f*) Prepsychotic physical and mental traumas
2. Initial stage of psychosis
   - (*a*) Age of onset
   - (*b*) Onset, insidious or sudden
   - (*c*) Exogenous precipitating factors
3. Symptoms of acute stage of psychosis
   - (*a*) Abundance or poverty
   - (*b*) Type of symptom pattern
4. Course of the disorder
   - (*a*) Steadily or gradually progressive from the beginning
   - (*b*) Form of "attack"—tendency to remission
   - (*c*) Catastrophic development
5. Physical disease components.

Studies following these lines of investigation have shown that certain combinations of factors in an essentially schizophrenic psychosis favor a good prognosis, while others indicate a poor prognosis, regardless of the type of general or special treatment afforded. Some combinations with a favorable prognosis are: pyknic habitus and cycloid temperament plus a presenting affect in the psychosis (particularly a depression); pyknic habitus plus cycloid temperament plus active exogenous precipitating factors, and athletic habitus plus schizoid temperament plus exogenous precipitating factors and amnesia for the acute phase.

Asthenic habitus plus schizoid temperament carries an unfavorable prognosis. asthenic habitus plus cycloid temperament means usually an unfavorable prognosis. The prognosis for children with schizophrenic-like personality and poor abilities is usually poor, as it is as a

rule for "clever" children with a schizoid temperament. Special abilities do not seem to help much.

There is evidence that persons with atypical forms of schizophrenia, or pseudoschizophrenic types, as they have been called, form a large percentage of the patients in various clinics and outpatient departments whose disease is diagnosed as schizophrenia or dementia precox. It is possible, if not probable, that herein lies the cause of the differences in reported therapeutic results, which are far more favorable for the pseudoschizophrenic than for the "nuclear," or genuine, form.

When the diagnosis is simply "schizophrenia," or dementia precox, a statement that 50 to 60 per cent of patients were cured or improved gives inadequate information concerning the relation of cure to therapy. Psychiatrists are in a clinical position to demand complete and accurate information as to the form of schizophrenia present. Only careful studies and precise statements will justify interhospital cooperation in a solution of the problems of schizophrenia.

DISCUSSION

DR. JAMES H. WALL, White Plains, N. Y.: Dr. Lewis has brought together some interesting points for consideration. In my experience, a significant factor in a good prognosis for a schizophrenic illness is a mature and evenly balanced personality. Often this is associated with more vigorous physical health. The more adequate the precipitating causes, the better the outlook. The preservation of the emotional attitude, of fighting off and not accepting the illness, no matter how deep the regression, is a good sign. The attitude of the relatives of schizophrenic persons plays an important role. Many of the patients who recover and improve to a notable degree are surrounded by mature, flexible and tolerant personalities in their families. So frequently the chance of restoration is interfered with by relatives who are inflexible and unteachable, and in their emotional thinking know more than trained psychiatric workers about what is best for the patient before, during and after the acute phase of the illness.

DR. PAUL FEDERN: I have only a few words to say about the impressive paper by Dr. Lewis, whose all-embracing experience covers the most varied cases. He was careful to follow up all the many factors of importance with cautious statistics. He demonstrated that there are a few conditions which allow one to expect a better than average course of the disease. Yet in the main a combination of factors is necessary to justify a good or a bad prognosis; a few specific combinations condition even an optimistic prognosis. I do not disagree with any statement of Dr. Lewis.

However, the psychiatric specialist, and even the head of a clinic, see cases of more advanced disease; rarely do his observation and his therapy begin early enough to influence the course of the illness from the beginning. For this reason, the prognosis with regard to psychotherapy, and especially psychoanalytic therapy, becomes different when based on experiences of the family physician or the practical psychoanalyst. One usually sees patients with early psychosis because of an error of diagnosis, but one can observe complicating factors from the beginning. By recognizing schizophrenia in the state of preliminary neurosis or when the first false conception of reality appears, one can treat and protect the patient in an early phase. I am convinced that such early diagnosis and treatment will influence the course and the prognosis.

One might learn to make the diagnosis even before false reality of thoughts and mixing of reality and unreality are established. Yet the patient is already aware of difficulty in maintaining the differentiation of thought and reality; the conception of reality temporarily ceases to be automatic; temporary and partial estrangement is felt. Sometimes the patient can overcome these disturbances by active attention; usually there is abnormal fatigue as the consequence of such attentiveness. I do not know what percentage of cases begins in this way. Also, I could not say that neurotic and prepsychotic estrangement are symptomatically different. Yet I have had patients remain in the stage of estrangement for twelve years.

The early phase of schizophrenia can be compared with the early beginning of tuberculosis in childhood. Since the protection and treatment of patients with early disease, the statistical aspect of tuberculosis has changed. Learning difficulties and behavior changes may be the first disturbance in schizophrenia; if one learns to recognize such first symptoms, the prognosis will improve. Meanwhile Dr. Lewis is to be thanked for having directed attention again to the multiple conditions of the developed process.

DR. JOHN G. LYNN: It is gratifying to have Dr. Lewis present in such a clear manner this outline of factors which seem to operate in the prognosis of schizophrenia. With reservations incidental to my own, more limited, psychiatric experience, I should like to mention a factor which, in my opinion, is of importance as an indicator of the prognosis and which I do not believe has been noted.

At McLean Hospital, Waverley, Mass., I noted that the schizophrenic patients who had had strongly developed visual orientation since early childhood, who manifested interest in manual and concrete activities in association with a lack of interest in verbal and auditory activities, seemed to have a better prognosis for recovery. Many of them were mechanically inclined, or they liked to draw or paint. In contrast, the schizophrenic patients who gave a history from early childhood of having a more auditory-verbal orientation, to the detriment of their visual and concrete interest, carried a poor prognosis and showed more rapid deterioration. The latter patients usually gave a history of being superior in languages and of having had musical interests, in preference to painting, drawing, sculpture or mechanical activities. Because of their predominant auditory-verbal orientation, it seemed easier for them to split off their abstract verbal levels from their concrete visual levels of thinking. As a consequence, any discrepancies between the content of their abstract verbal level and the content of concrete visual level of perception was not so noticeable or disturbing to them. In fact, their abstract verbal level seemed to operate, in an omnipotent way, almost entirely as an agent of wishful thinking, relatively free from the normal necessity of contemporaneously maintaining some degree of structural or factual correspondence with concrete visual reality.

Did Dr. Lewis observe that a more concrete visual orientation was a good prognostic sign, and a more auditory-verbal orientation a poor prognostic sign, in schizophrenia?

DR. NOLAN D. C. LEWIS: My paper is composed chiefly of conclusions. It should follow the evidence which led to these conclusions. The material on which my studies were based consists of more than 1,000 cases, and the impressions presented here were based on a series of 600 cases. The material when published in full will contain this evidence.

Dr. Lynn stated in language that one can understand his impressions of the prognosis for patients with a strongly developed visual orientation. It has always seemed that such persons have a greater diversity of interests than those who are interested in, and who think characteristically in terms of, abstract processes. It is recognized that the presence of visual hallucinations in a case of schizophrenia is usually a favorable prognostic sign. It often indicates an active toxic element in the situation, while the common auditory hallucinations are more malignant and more characteristic of the nuclear, or central, type of schizophrenia. Many of the persons who break down are those who spend a great deal of their time in a more circumscribed environment, in a self-imposed isolation, where they build up a world of their own, and if they avoid a full blown schizophrenia and get started along lines of creative thinking, they may become efficient librarians or college professors. Certain of the expressions or symptoms of schizophrenia act as a healing process to save the patient from regressing too far or becoming completely dissociated, and thus are constructive forces. Many patients struggle to hang on to reality as long as they can before slipping into a deep psychosis. Symptoms may represent healing tendencies, and if one knew in the early stages how to time the therapy just right, or which symptoms to support as aids to healing, one might help greatly in the correction of the disorder. As in other pathologic processes, when some of the somatic pathology is an attempt of the tissue to repair damage, one should attempt to promote any action which preserves the healing tendency.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

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Intelligence Following Prefrontal Lobotomy in Obsessive Tension States.

DR. JAMES W. WATTS and DR. WALTER FREEMAN.

In 1938 we reported on the results of interruption of the frontal association pathways in 6 patients with obsessive tension states. We have continued our studies on these and similar patients, and now we can amplify our conclusions, based on 45 patients studied from one to seven years after operation.

Prefrontal lobotomy relieves nervous tension and obsessive thinking. After operation the patient may still cling to the idea that he has tuberculosis or syphilis or that his eustachian tube is stopped up. A woman may look in the mirror and see just as much hair on her face and arms as before operation, when she thought that suicide was the only solution. But if the idea no longer is accompanied by a heavy emotional charge, it loses its importance and no longer dominates the patient's life.

In the 45 patients under discussion, it was the emotional charge, therefore, that caused the disability, rather than the peculiar ideas themselves. Furthermore, there was no significant deterioration, either intellectual or emotional. Although the average duration of symptoms of these patients was slightly more than ten years, only 5 had been confined to hospitals for mental disease.

If brain-damaging therapeutics is to be employed for patients without mental deterioration, it is important to know how the intelligence is affected by the procedure. If relief of mental pain is secured only by sacrifice of the intelligence and understanding, the price is too great.

According to the "Encyclopedia Britannica," "Intelligence of understanding is a term that is still used by psychologists with considerable latitude of meaning. Sometimes it is used as a synonym of 'cognition,' that is to say, it is applied to any of the numerous processes by which knowledge is built up. Sometimes it is restricted to the conceptual process, as distinct from the process of sense perception. Some [psychologists] frankly admit that they do not know and do not care what this 'intelligence' may be which they are measuring, so long as these measurements can be made use of. Lastly, ordinary everyday usage perhaps tends to emphasize the practical character of intelligence as consisting in the ability to employ the right means in order to achieve the various ends pursued."

In this paper, we are concerned with the practical character of intelligence, and if our yardstick of intelligence is "the ability to employ the right means to achieve the ends pursued," then it would appear that our patients are more intelligent after lobotomy than before. Before operation, only 17 per cent were leading useful lives; 13 per cent were employed; 2 per cent were employed part time and 2 per cent were housekeeping. At present, 67 per cent are leading useful lives; 38 per cent are employed; 11 per cent are employed part time, and 18 per cent are housekeeping. The statement does not imply that the patients are restored entirely to normal, for many show personality changes indicative of frontal lobe deficit, but 67 per cent are now employing their ability in a manner to achieve the ends pursued, as compared with 17 per cent prior to operation.

Persons with obsessive tension states have energy and ambition; they are meticulous, economical and punctual. While they may not always be agreeable, they are good workers and often find that their old positions have been held open for them if they have not been away too long. On returning to work, they are usually slow for a while, but accurate, and perform their duties to the satisfaction of the employer. Most of the patients seek work in the same type of employment in which they had been engaged before lobotomy. A few may change occupations, like a clerk in the Treasury Department, who had never liked anything about his job except getting his pay check twice a month. Radio had always been his hobby, and after operation, still finding work in the Treasury Department obnoxious, he resigned and became a radio operator. At present he is teaching the mathematics of radio in the Signal Corps.

Patients in this group come seeking lobotomy, in contrast to patients with involutional depressions, who are virtually dragged in by their relatives. They believe that if they can be freed of nervous tension they can apply themselves to their tasks and reach their goals. Prefrontal lobotomy relieves nervous tension and often aids the patient in achieving the end he pursues. For persons who have set their goal too high, lobotomy brings it closer, but does so by making them more easily satisfied with their accomplishments. It makes them willing to do work commensurate with their abilities.

DISCUSSION

LIEUT. PAUL J. SCHRADER: I agree with Dr. Watts and Dr. Freeman in their observations on the intelligence after lobotomy. My colleagues and I have now checked the intelligence of about three fourths of all the patients on whom we have operated, and, so far as I know, intelligence is not significantly disturbed.

We have no preoperative standard. These patients do surprisingly well after operation, even the schizophrenic group. There were 208 patients, of whom about 88 per cent were schizophrenic with institutional practice. I continue to be astounded by the letters I get from relatives, who say, "Well, John is working now. John is doing well." Well, I know that John had been in the state hospital for several years. What is intelligence? If it is the functional capacity, then on the whole prefrontal lobotomy does not disturb it. However, the worst, I should say the most unfortunate, results were in the obsessive group with tensions.

A professor of a midwestern university had a conceit which he was able to hide from his family; after operation he had complete loss of social sense, and we had to commit him to an institution. In our entire series of patients his was the only unfavorable result. Yet his intelligence was undiminished. His social sense was, I should say, lost. The operation had not aided him, but the results with the obsessive tension states were impressive. I believe that the procedure is about as specific a treatment as can be given for these obsessive tension states.

I am entirely in accord with Dr. Freeman and Dr. Watts in their statement that, judging by all means now available, intelligence itself is not diminished by prefrontal lobotomy.

DR. HERBERT FREED: The authors spoke of a patient who had psychoanalysis and reported their experience with other patients. How many of them try intensive psychotherapy after operation, and how do they take it? Do they seem to gain insight into their obsession with intensive psychotherapy? Do the authors use it? Do they advocate its use after the lobotomy?

DR. WALTER FREEMAN: In answer to Dr. Freed's question, I know of only 1 patient who had psychoanalysis after operation. Five had a rather formal psychoanalysis before operation, the periods ranging from eight months up. One man had fifteen months of psychoanalysis before operation, without any significant progress. A young woman had had psychoanalysis before lobotomy, without any progress at all.

The reaction of the patients to postoperative psychotherapy is not good because they are so free or so devoid of all introversial feelings and of all interest in themselves. It is practically impossible to get them to pay attention to their various mechanisms. Lobotomy makes introspection especially difficult. These patients would rather talk about the weather, what they are going to do or where they are going to go. Their attention is devoted to outward manifestations, and they seem not to like to discuss their symptoms any more.

DR. FRANCIS C. GRANT: I have had no experience with lobotomy in treatment of the obsessive and ruminative states. The largest number of patients on whom I have operated had a manic-depressive psychosis. For these patients lobotomy was effective, although, seemingly, as much now can be accomplished by electric shock therapy. Recently I have had the opportunity of operating on a number of schizophrenic patients. The results have varied directly with the mentality of the patient prior to operation. If the patient was violent and mentally dilapidated before operation, his violent attacks will in great measure disappear after operation, and the amount of useful intelligence he has may seemingly increase. But he will never have a normal intelligence. Unquestionably, in my experience, lobotomy blunts the intelligence. After operation the patient may seem more active mentally, but that is because lobotomy enables him to make better use of what he has left.

DR. RUDOLPH JAEGER: I wonder if there is any reason for arguing whether or not the intelligence of these persons is increased by lobotomy. It is a matter of whether or not the intelligence that they have can be made to work. For example, one youngster with catatonic dementia precox on whom I had operated had been in hospitals for psychopathic patients for many years. He was absolutely useless and had to have constant nursing attention. Since the operation he has been able to work in a pawnshop and has carried on now for three years, doing first-class work. Now one might say this patient had more potential intelligence before he was operated on and that the lobotomy may have reduced this intelligence, if there were accurate methods of measuring his brain capacity, but certainly he was not using his intelligence for any practical purpose. No matter how intelligent a person, if that intelligence is not properly used it is of no practical value. This is certainly true of most of the patients with obsessive tension. I have had only a small number of patients, perhaps not enough even to comment on the results.

I have had only 10 patients with mental disease on whom operation was performed prior to a year ago. The oldest patient, operated on more than three years ago, had an obsessive tension state. She was forced on me by my friend, Dr. Walter Freeman, and her family. Her condition has greatly improved, and she has gone back to her home and is able to carry on her household duties as a capable wife. Before the operation she was a total loss to her family. She may have been ever so intelligent, but certainly she was not using her intelligence to any degree of efficiency.

Of my 10 patients on whom prefrontal lobotomy was done, 6 had obsessive tension states. One of these 6 died of senile complications three months after the operative procedure. One of them showed no improvement. Four could be called almost completely cured. All of them had had shock therapy and prolonged treatment in hospitals for psychopathic patients. The 4 cured patients were among the first I had, and their improvement was remarkable. There were 4 patients with schizophrenia in my series. Three of them were greatly benefited, and 1 failed to improve. I have a great deal of enthusiasm for prefrontal lobotomy in selected cases of mental disease. The improvement following operation is a thing one cannot overlook when one compares the condition before and after the procedure.

DR. JAMES W. WATTS: Among the numerous definitions of intelligence, we have chosen as a yardstick "the ability to employ the right means in order to achieve the various ends pursued," and we have emphasized its practical character. If one uses a different definition of intelligence, then one might arrive at a different conclusion.

In answer to Dr. Grant's question, I believe it is more difficult to arrive at a conclusion about intelligence in schizophrenic patients, as there is a tendency for many of them to deteriorate. If they do deteriorate, it is difficult to say whether deterioration is due to the disease or to the operation. Patients with obsessive tension states are better material for study of this problem; our patients rarely showed evidence of deterioration, even though the average duration of symptoms was ten years.

Electroencephalographiic and Pneumoencephalographic Studies of Multiple Sclerosis. DR. WALTER FREEMAN and DR. ROBERT COHN, Washington, D. C.

Fifteen cases of multiple sclerosis have been studied by pneumoencephalography and 6 cases by electroencephalography, 4 of the 15 cases being studied by a combination of the two methods. The pneumoencephalographic findings consist of asymmetric dilatation of the ventricles and irregular stellate shadows and large striations over the surface of the brain, occasionally symmetrically located. A characteristic position is the medial aspect of the hemisphere. Increased air in the posterior fossa, especially around the pons, is seen in some cases; the fourth ventricle may be dilated and the cerebellar folia show up prominently. Encephalograms made at intervals may show increased enlargement of these air shadows, particularly in the third ventricle. *In some cases of long duration of the disease* the changes are minimal.

The electroencephalogram was abnormal during an acute exacerbation in only 1 case, and as the condition went on to remission the electroencephalogram also became normal.

Autopsy was performed in 4 cases, and comparison of the photographs of the brain with the roentgenogram shows a fair degree of correlation of the shadows with the sinking in of the cortex due to destruction and cicatricial contraction of the subcortical white matter. Histologic study of the brains indicated that the pathologic process in disseminated sclerosis may destroy with relative completeness the subcortical white matter and yet leave the cortex almost entirely unaffected except for the radial fibers.

It is concluded that the pneumoencephalographic findings are due not to local cortical atrophy but to sinking in of the cortex following cicatricial contraction of the subcortical white matter, and that the electroencephalogram, which is normal, shows a high correlation with the preservation of architecture of the cerebral cortex.

DISCUSSION

DR. MICHAEL SCOTT: In 1936 I presented at a meeting of this society (ARCH. NEUROL. & PSYCHIAT. **38:** 218 [July] 1937) 6 cases of multiple sclerosis in which the encephalographic changes were practically identical with those described by Dr. Freeman tonight. The roentgenograms showed predominantly dilatation of the ventricular system and increased sulcus markings in the frontal lobe, in the parietal lobe especially and in the cerebellum. In all these cases large amounts of cerebrospinal fluid, often in excess of 200 cc., were removed at the time of the air studies.

DR. SAMUEL B. HADDEN: Dr. Scott's mention of his cases has refreshed my memory. I think he will recall that in discussion of his presentation I showed roentgenograms in cases of a condition clinically diagnosed as cerebellar ataxia; in these cases the findings were much the same as in Dr. Scott's cases and in those which Dr. Freeman presented tonight.

DR. MATTHEW MOORE: Dr. Freeman's contribution is important, it seems to me, because he has again demonstrated that by means of pneumoencephalographic studies one can correlate intravitam cerebral changes with gross postmortem observations, rather than because of his intimation that multiple sclerosis has a specific encephalogram.

In 1934-1935 I presented a series of 152 cases of various types of psychoses, of both organic and nonorganic origin, in which pneumoencephalographic studies had been made. Among these were many instances of schizophrenia, epilepsy and early dementia paralytica in which the cortical atrophies were similar in many respects to the changes Dr. Freeman has shown. With dementia paralytica, there is supposedly a characteristic pneumoencephalogram. However, this is not entirely true, as there are essentially two types: one showing intense, spotty cortical atrophy with dilatation of the ventricular system, and the other presenting the so-called ground-glass appearance of the hemisphere with pronounced symmetric or asymmetric dilatation of the lateral ventricles. I do not believe that a specific pattern exists with multiple sclerosis or Freidreich's ataxia, as has been suggested by Dr. Hadden, and it would be difficult indeed, without clinical data, to make a definitive diagnosis on the basis of the pneumoencephalogram alone. The results of air studies can be interpreted only as a reflection of the changes occurring within *the cortex or subcortex, with the secondary manifestations* in the configuration of the surface of the brain and the ventriclular system resulting from atrophies and contraction of the tissue.

DR. N. W. WINKELMAN: Dr. Freeman has portrayed vividly the recognized underlying morbid process in multiple sclerosis. One could have surmised that there may be ventricular inequality, and at times dilatation, for one of the characteristics of multiple sclerosis is the periventricular location of the characteristic patches of sclerosis. It is also known that the morbid process is as a rule located beneath the cortical gray matter, and not within it. The complete disappearance of the myelin sheaths from one area of the subcortex with preservation of the U fibers, shown in one of the slides, is unusual in a case of multiple sclerosis. It is more commonly seen with other demyelinating diseases, such as Schilder's.

Knowing, therefore, that the morbid process of multiple sclerosis is subcortical, and not cortical, one is not surprised to learn that there is little or no change in the electroencephalogram. One could not, therefore, make a diagnosis of multiple sclerosis on the basis of the brain wave pattern.

DR. WALTER FREEMAN, Washington, D. C.: In the last case, in which the subcortical tissue was apparently so devastated, an encephalographic examination was not made. I do not know why the electroencephalogram is normal in cases with destruction of areas of the subcortical tissues and with the slot effect in the encephalogram, unless it is that the cortex is anatomically intact. The cell bodies themselves and the intracortical connections apparently keep up this wave pattern through the cortex.

Is the encephalogram specific for multiple sclerosis? I do not think so. It is only suggestive of the disease. My associates and I have made a diagnosis of multiple sclerosis in 2 cases of an obscure condition by finding such stellate shadows over the cortex. I am willing to grant that Friedreich's ataxia causes atrophy of the cerebellum. I am interested to hear that the atrophy also involves the parietal area in this disease, for I have not observed it. Even so, I should expect the air, or the atrophy, whichever one prefers to call it, to be symmetrically distributed over the cortex in cases of Friedreich's ataxia, whereas asymmetry is the rule with multiple sclerosis.

In cases of dementia paralytica there is another complication, for the meningeal infiltration may cause loculation of the air and variable filling of the subarachnoid spaces. That does not often happen in cases of multiple sclerosis, although it did occur in 1 or 2 cases of the

series. With dementia paralytica there is usually dilatation of the ventricles, but my experience has not been large.

Neonatal Toxoplasmosis. Dr. N. W. Winkelman and Dr. Matthew T. Moore.

Human infection with Toxoplasma hominis has recently created interest because of an increasing awareness that this condition is probably more prevalent than the relatively small number of cases recorded in the literature would indicate.

In the infantile form, manifested chiefly as encephalitis or meningoencephalomyelitis, there is increasing evidence that the infection is of antenatal origin and that it is transmitted to the fetus via the mother. It is not unlikely that some stillbirths and deaths of 1 or 2 day old infants have been due to unrecognized toxoplasmic encephalitis. Although the cerebral lesions may be severe and extensive, some patients survive beyond infancy.

Briefly, the clinical diagnostic criteria are as follows: (1) history of onset of symptoms at birth or early infancy; (2) varied neurologic symptoms, including convulsions; (3) internal hydrocephalus or microcephaly (the latter being infrequent); (4) focal necrotizing chorioretinitis; (5) roentgenographic evidence of scattered intracranial calcifications; (6) pneumoencephalographic evidence of internal hydrocephalus; (7) mental retardation (not invariably); (8) xanthochromia, pleocytosis of round cell type and high total protein content of the spinal fluid; (9) recovery of toxoplasmas from the blood or cerebrospinal fluid by animal inoculation (mice, rabbits), and (10) demonstration of neutralizing antibodies in the blood of the infant or mother.

Up to the present 11 cases of fatal infantile toxoplasmic encephalitis (Steiner) have been reported, the following case constituting the twelfth.

REPORT OF A CASE

A premature male infant, delivered of a 28 year old primiparous, diabetic mother, became cyanotic two days after birth and had difficult, spasmodic breathing and pronounced jaundice. Fine petechial hemorrhages appeared in the skin. Tremors and twitchings of the fingers and feet were present, and later, during the night, convulsive movements occurred. Examination showed enlargement of the heart, liver and spleen. The clinical picture suggested the presence of erythroblastosis fetalis. On the third day of life the infant suddenly stopped breathing and died.

Necropsy showed icterus, petechial hemorrhages of the skin, splenomegaly, hepatomegaly and undescended testicles. The spleen was three times the normal size, and the liver, which weighed 150 Gm., showed numerous areas of "fatty" degeneration.

The brain, at the time of removal, showed evidence of internal hydrocephalus. The lateral ventricles were moderately dilated. Widely distributed areas of necrosis appeared in both temporal and frontal lobes, the floor of the lateral ventricles and both basal nuclei. Many of the degenerated areas were periventricular.

Histologically, the necrotic lesions which were seen on gross inspection showed all the characteristics of a granuloma plus the deposition of calcareous granules.

The granulomas themselves, with the cell stain, showed three distinct zones: an inner one of necrotic material, a middle zone of granulation tissue and an outer area of tissue reaction. The middle zone was composed of chronic inflammatory elements (lymphocytes, monocytes and plasma cells); fibroblasts; epithelioid cells; large vesicular cells containing debris; occasional polymorphonuclear leukocytes, and a protozoon (Toxoplasma), occurring in cysts, free in the tissue and in phagocytes.

Some of the lesions in the temporal lobe, the cingular gyrus and the hippocampus involved the leptomeninges, and the cellular exudate in the subarachnoid space consisted of chronic inflammatory elements—lymphocytes, plasma cells and monocytes. The toxoplasmas were not present in the subarachnoid space.

The toxoplasmas were seen in and around the granulomas except in the necrotic portions. The appearance of the organisms themselves corresponded in all essentials to that described in the literature. None of the organisms could be seen in ganglion cells. The leptomeninges in the unaffected portion of the brain showed no inflammatory or proliferative reaction.

Our patient was an 8 month premature infant who lived three days. The brain for the most part showed massive granulomatous lesions and no granulomas of the miliary type described by Wolf, Cowen and Paige, Sabin and others. It is evident from the examination of our preparations that the lesions were chronic and antedated the elective cesarean delivery by weeks, if not months. This, obviously, represents a true antenatal type of infection of the brain.

DISCUSSION

Dr. Gabriel Schwarz: I have been interested in toxoplasmosis because there has been an opportunity at the University Hospital to see cases of the arrested disease. Since I reported 2 cases before this society, I have seen 2 others; I have now studied 4 cases of arrested toxoplasmic encephalitis.

Were Dr. Moore and Dr. Winkelman able to culture the toxoplasms by inoculation of mice? Did they send a specimen of serum to Dr. Wolf and his group for neutralization tests? There is certainly needed a more definite test than the neutralization test developed by Sabin. In both cases that I studied at the University Hospital, and in which I sent specimens of serum to Dr. Wolf, some of the control specimens were positive, not so strongly, but certainly positive.

This case reported by Dr. Winkelman and Dr. Moore increases the number of well studied and authenticated cases of toxoplasmosis of the nervous system. I think this condition will be found the cause of more fetal and infantile deaths in the past than has been supposed.

Dr. George Gammon: Was there evidence of kernicterus in this child? Was he jaundiced, with enlarged liver and spleen and erythroblastosis?

Dr. N. W. Winkelman: We did not make any injection experiments on animals because the brain was sent to us after fixation in solution of formaldehyde. The child's mother moved after her discharge from the hospital, and we have no trace of her. In answer to Dr. Gammon's question, the child had the icterus that one sees in many newborn children. It was not icterus neonatorum gravis, and the brain showed none of the changes of the so-called kernicterus.

Dr. Matthew Moore: As Dr. Winkelman stated, the specimen was submitted to us in poor condition, and it was not until histologic studies had been made that the diagnosis became apparent. In order to fulfil all the criteria for the diagnosis of toxoplasmic meningoencephalitis, we should have desired serologic tests on both the infant and the mother; however, this, obviously, was not possible. As was stated in the paper, observers have tested not only the patient and mother for serologic reactions, but other members of the family,

who, surprisingly, have showed a positive reaction for toxoplasmic infection. A representative number of persons from the lay population have had serologic tests for the toxoplasmic infection, and many have given a positive reaction. It is not at all unlikely that toxoplasmic infection in adults is fairly prevalent, but the human adult acquires immunity to the organism and therefore does not manifest clinical signs. In the fetus, however, to which the organism has been transmitted by the mother, there appears to be a susceptibility of the nervous system to the ravages of the organism, and the characteristic meningoencephalomyelitis develops.

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

H. M. ZIMMERMAN, M.D., *President, in the Chair*

Annual Meeting, May 18, 1944

Porencephaly. DR. OTTO MARBURG, New York.

A study of the literature on porencephaly reveals two different concepts, one which acknowledges as porencephaly only the condition in which a cavity in the brain connects the ventricle and the subarachnoid space, and the other which considers every simple cavity as constituting porencephaly (incomplete porencephaly, or pseudoporencephaly). The second concept is based on the fact that these simple cavities occur in the same site and present the same pathologic changes as true porencephaly. Surprisingly, the site of the cavities corresponds with the drainage areas of the veins, particularly that of the vena magna Galeni. This fact was proved by the investigations of Siegmund and, in particular, by those of Schwartz. The drainage areas of the respective branches of the veins are well known, as a result of the studies of Schwartz and Fink and Schlesinger. The vena terminalis anterior and the vena lateralis ventriculi are particularly affected, the whole drainage area of the vena magna Galeni being occasionally involved, thus causing cavities within the cerebellum and, via the vena basalis of Rosenthal, at the base of the brain, including the optic chiasm and the optic tract. Involvement of the latter area explains the occasional occurrence of optic nerve atrophy. The intactness of the striopallidum in the majority of the cases under discussion is evidence that there involvement of the arteria cerebri media, as has been suggested by many authors, did not occur. There may, however, be a few isolated cases in which arterial obstruction leads to similar formations.

The cortical foci are cone shaped, as was first demonstrated by Schwartz. Since the veins accompany the arteries, it is obvious that in the frontal area, as well as in the sylvian fissure, the cavities are horizontal, whereas they run dorsoventrally in the region of the central convolutions. The destructive process leading to the formation of the cavity is a necrotic or malacic one, occasionally accompanied by lymphocytes around the blood vessels, due to stasis edema. This, however, is not proof that an inflammatory process is the cause of porencephaly, as was suggested by Strümpell. Concerning this point there is great confusion, since what is called Virchow's encephalitis is in reality malacia following phlebothrombosis or phlebostasis (Wohlwill). This condition is a usual accompaniment of porencephaly. When, however, there is another type of inflammation, either a complicating factor (secondary infection, as in the case of Globus) or phlebothrombosis (as in a case of Ghiberti) causes the destruction. That arrested development is a cause of porencephaly, as was first suggested by Heschl, was disproved by Zingerle, with sufficient evidence. Recently Yakovlev and Wadsworth have tried to bring new evidence in favor of Heschl's suggestion. The course of the clefts, corresponding in their opinion, to zones of cleavage, or primary fissures, depends, as already explained, on the site of the veins. The relation between pia and ependyma is of no significance, since the latter has its own circulatory mechanism, and it is questionable whether the cover of the porus is formed by arachnoid or by newly formed connective tissue. Microgyria is seen in every case of porencephaly, and dystopias are easily explained by the time of onset of the porencephaly. The earlier the onset, the more dystopias will be encountered.

For the formation of porencephaly there must be, in addition, hydrocephalus, with perforation of the thin walls of the cavity. This hydrocephalus is not primary, but is secondary to some lesion of the brain, as d'Abundo and I have proved experimentally.

DISCUSSION

DR. CLEMENS E. BENDA, Wrentham, Mass.: Dr. Marburg has used the term porencephaly for a number of different conditions which should be kept distinct. He uses the term for true porencephaly, which is a congenital malformation developing some time during the second half of the prenatal period, and for the cystic degeneration of the brain which may be the product of birth injury or of infantile encephalitis. These various conditions have different causes, and it is hard to understand an attempt to explain the various operative factors by a single mechanism.

DR. OTTO MARBURG, New York: The term "congenital" does not mean endogenous; even if porencephaly is assumed to be congenital, it still may be due to an exogenous factor, such as trauma to the mother which affects the fetus (Seitz, L.: *Arch. f. Gynäk.* **83**:701, 1907. Jaffé, R. H.: Traumatic Porencephaly, *Arch. Path.* **8**:787 [Nov.] 1929).

Influence of Gonads and Adrenal Glands on the Chemical Composition of the Brain. DR. A. WEIL, New York, and DR. R. A. GROAT, Chicago (by invitation).

It had been shown in previous publications that there is a difference in the phospholipid content of the brain of male and female white rats, which changes during growth and after removal of the gonads. A similar difference was demonstrated between the brain of man and that of woman. The present investigation is concerned with the effect of injections of synthetic estrogen and androgen on the chemical constitution of the brain of the white rat. Testosterone propionate and α-estradiol benzoate were injected into both normal and gonadectomized rats. Injections of homologous "sex hormones" into normal animals did not change the chemical composition of their brains. If, however, the preparation was injected into immature gonadectomized rats, there was a change in the direction of the normal makeup. Heterologous "sex hormones" changed the chemical composition of both normal and gonadectomized rat brains toward the female or the male side respectively. It was more difficult to influence the chemical composition of adult rat brains through the injection of synthetic androgen or estrogen in both normal and gonadectomized rats.

In an attempt to ascertain the influence of other endocrine glands on the brain, changes in the latter organ following ablation of the adrenals were studied.

After removal of the adrenal glands in both male and female white rats, there were an increase in the weight of the brain of more than 10 per cent and a proportional increase of the various chemical constituents, without any qualitative changes. At the same time, the weights of the kidneys, heart, thyroid, testes and prostate were increased proportionally, the hypophysis not being affected.

For more than two hundred years it has been known that congenital aplasias of the cerebral cortex accompanied by atrophy of the hypophysis in man is frequently associated with atrophy of the adrenal glands. Various theories center about primary involvement of either the cerebral cortex or the adrenals. However, the fact that ablation of the adrenals results in enlargement of the brain vitiates the theory which designates the primary role to the adrenals. After hypophysectomy the weight of the adrenal glands is reduced to less than one-fifth their normal weight. Hence it would seem that the atrophy of adrenal glands in cases of hemicephaly or cortical aplasias in man is due to atrophy of the hypophysis, and not of the cerebral cortex.

Acute Fatal Experimental Toxoplasmosis in a Young Monkey. Dr. D. Cowen and Dr. A. Wolf, New York.

The source of human infection with toxoplasmas is probably the large reservoir of toxoplasmosis in rodents and birds. Occasionally, spontaneous infection with this protozoon has been noted in other species. In view of the increasingly frequent recognition of toxoplasmosis in man, it is of interest to note that the disease has not often been observed in other primates.

Spontaneous toxoplasmosis was reported in a monkey (Stentor senilicus) by Thézé, in a baboon (Cynocephalus) by Levaditi and Schoen and in a chimpanzee by Kopciowska and Nicolau. These observations consisted essentially in the chance identification at autopsy of rare and isolated parasites without lesions. The organisms occurred in the brains of 2 animals, and in the bone marrow, spleen and liver, in another. Since 2 of the animals had been inoculated with rodent tissues for other purposes, one is justified in doubting whether the toxoplasmas had not accidentally been introduced.

Since 1909, several attempts have been made to infect primates experimentally by Nicolle, by Levaditi and by Sabin and their various co-workers. Several species of monkeys (Macaca cynomolgus, Macaca sinicus, Macaca rhesus and Cercopithecus patas) and 2 baboons (Papio sphinx) were inoculated with toxoplasmas by various routes, chiefly the intracerebral. For the most part, single representatives of each species were used, and negative results were obtained. It has been shown, however, that adult Macaca rhesus monkeys may manifest clinical and serologic evidence of a mild, transient infection. Pathologic examinations carried out on 3 monkeys and a baboon gave negative results. In brief, a fatal infection in primates has not yet been produced.

In the present experiments, 7 Macaca rhesus monkeys were inoculated by the intracerebral and other routes with human strains of Toxoplasma. Of these animals, 2 were immature, 7 months of age; 2 were young adults; 2 were adult pregnant females, and the last, an infant, inoculated at 2 months of age, was the offspring of one of the 2 females. An adult baboon was also inoculated. One immature monkey, given inoculations of the brain and the peritoneal cavity, had repeated convulsions and died five days after intracerebral inoculation. Autopsy revealed meningoencephalitis, interstitial myocarditis, focal interstitial pneumonitis, focal myositis and small inflammatory lesions in the rete testis. The second immature monkey probably had transient acute toxoplasmosis, from which it recovered. This monkey's serum gave a weakly positive neutralization test for toxoplasmas, but the animal showed no lesions when killed five months later.

All the other animals showed no evidence of toxoplasmosis, either clinically or at autopsy. Of the animals tested serologically, the baboon and 1 monkey gave negative reactions and the 2 pregnant females mildly positive reactions. The attempt to transmit the infection to the fetus by infecting these pregnant monkeys was unsuccessful, but the infant born of 1 of them proved refractory to infection by repeated inoculation. In conclusion, only in 1 immature monkey did a fatal infection develop. This susceptibility of a younger animal is interesting in view of the higher incidence of human toxoplasmosis in the first decade of life.

Histopathology of Cerebral Aneurysms. Dr. F. M. Forster, Wellesley, Mass. (by invitation) and Dr. B. J. Alpers, Philadelphia.

In previous studies on congenital aneurysm a question arose as to the congenital nature of the defect of the media, and the status of the elastica and of the intima was not clearly defined. For this reason, 8 aneurysms of the circle of Willis, all occurring at bifurcations, were studied in serial sections. Hematoxylin and eosin, Van Gieson's stain for elastic tissue and Masson's trichrome stain were employed. All 8 aneurysms arose from an area of defect in the media of the parent vessel. These defects in the media were sharply defined and had not undergone inflammatory or degenerative changes. Study of these defects in serial sections gave evidence that they were not artefacts due to tucking in of the media. In none of the 8 aneurysmal sacs was there any evidence of a medial coat. In contradistinction to this, the condition of the elastic membrane was variable. In 1 specimen it was present and complete in the aneurysmal sac. In 2 specimens the elastic membrane of the aneurysmal wall was entirely lacking, and in 1 of them the elastica of the parent vessel ended abruptly at the point of origin of the aneurysm. In 5 of the aneurysmal sacs elastic tissue was present in varying amounts, but as fragmented strands. In these 5 aneurysms and in 1 of the aneurysms in which the elastica was lacking, the elastic membrane of the parent vessel as it approached the origin of the aneurysmal sac became frayed and split. In 4 of the 8 aneurysmal sacs the intima was normal, and in the remaining 4 sacs it had undergone proliferative and degenerative changes. Changes in the intima and alterations of the elastica were not necessarily coexistent, and either occurred independently of the other.

In view of the constancy of the defect of the media and its freedom from evidence of degeneration or inflammation, it is concluded that the cerebral aneurysm is a true congenital defect. The wide range of alterations of the elastic membrane, from a complete membrane through fragments of elastic tissue to entire absence of such tissue, occurring irrespective of other degenerative changes, indicates a tendency of the elastica to disintegrate in the wall of the congenital aneurysm. In view of the wide range of alterations in the elastica, it is concluded that, regardless of the state of the elastica, such aneurysms should be considered congenital.

DISCUSSION

Dr. Alfred Angrist, Jamaica, N. Y.: The variations in the defects which have been stressed are

enlightening, for heretofore authors have emphasized a defect in one particular coat or another of the vessel, to the exclusion of others. If any one coat of a blood vessel is to obtain undue emphasis, it would seem proper to call attention to the necessity of an intact elastica if aneurysmal bulging, due to increased pressure within the lumen of the vessel, is to be avoided.

It is of interest that the authors noted defects in so-called arteriosclerotic aneurysms. This is in keeping with the observations which my associates and I have made and permits of a unifying concept. It is our impression that many so-called arteriosclerotic aneurysms are basically congenital lesions, and that such congenital lesions have an increased propensity to undergo arteriosclerotic changes of a degenerative nature. It is such changes that lead to the softening and weakening of the sac and to actual rupture and hemorrhage. In all of the congenital aneurysms studied which led to fatal subarachnoid hemorrhage we invariably noted arteriosclerotic changes. It is of interest that occasionally we saw active arteriosclerotic changes with lesions simulating a necrotizing process, or a condition similar to that often observed in the arterioles with malignant nephrosclerosis. Aneurysms which in the gross seemed purely congenital, on microscopic examination showed arteriosclerotic changes, and often acute necrotizing lesions in the wall. According to this concept, the hemorrhage, which is the dramatic complication of these lesions, is explained by the selective localization of the general pathologic process of arteriosclerosis in the aneurysmal sac, while the rest of the vessel usually fails to show such changes. Whether the arteriosclerotic process is brought on by the physical effect of eddies and the stresses in the sac remains a theoretic consideration. The arteriosclerotic process then becomes the basis for the rupture of the congenital aneurysm, much as it is accepted as the basis for ordinary apoplexy.

Giant Cells in Neuroectodermal Tumors of the Brain. Dr. J. H. Globus, New York, and Dr. H. Kuhlenbeck, Philadelphia.

As far back as 1905, the presence of giant cells in gliogenous tumors was described by Babes, and later the observation was confirmed by other authors. In 1918 and 1924 Globus and Strauss studied the type of tumor which they designated as spongioblastoma, and later as spongioblastoma multiforme. Their observations emphasized the role played by giant cells in rapidly growing gliogenous tumors. It was suggested by these authors that the rapidity with which such a tumor grows is related to the presence of these giant cells. From other quarters, however, a theory was advanced that these cells are reactive elements, provoked by necrobiosis. On the other hand, experimental work with tissue culture has in the meantime provided new evidence that the giant cells are a special cell form which can be reproduced in artificial growth mediums.

An attempt to emphasize the importance of giant cells was made by Farnell, in collaboration with Globus, but his preliminary report was based on less abundant material.

Having in the course of the past twenty years collected abundant material from which to choose striking examples of various types of giant cells in various stages of development, we selected 35 neoplasms displaying characteristic varieties of giant cells. These neoplasms belong to seven types of neuroectodermal tumors of the brain: spongioblastoma multiforme, spongioneuroblastoma, spongioblastoma ependymale, transitional glioma, transitional glioneuroma, tuberous sclerosis (spongioneuroblastosis disseminata) and pinealoma.

In this material the formation of giant cells both by true mitotic division and by atypical multipolar mitosis was observed. Tripolar, tetrapolar, pentapolar, and possibly hexapolar, metaphase stages, with the corresponding number of centrosomes, were noted. Other giant cells, however, showed evidence of amitotic nuclear division. Highly irregular amitotic fragmentation and break-up patterns of nuclear material were observed in some instances, while in others the amitotic nuclear, constriction and division figures resembled those seen in normal tissue. On the other hand, phases of explosive mitotic activity leading to rapid tumor growth were noted. True giant cells of spongioblastic, as well as of neuroblastic, lineage were recognized in areas untouched by necrobiotic processes. Multinuclear, as well as mononuclear, giant cells were observed in both spongioblastic and neuroblastic categories. The close relation of such giant cells to the monster cells in tuberous sclerosis (spongioneuroblastosis disseminata) could be demonstrated. Giant cells show not only features of arrested or retarded differentiation, but progressive changes in the direction of further differentiation (Nissl substance, neurofibrillae or astrocytic features).

The sites of predilection of tumors rich in giant cells were the subependymal cell plate, the region of the sulcus terminalis and other sites of embryonic remnants which we have described in previous communications.

In cases of spongioneuroblastoma rounded groups of large neuroblastic cells surrounded by spongioblastic elements could be seen. Individual neuroblastic cells might even appear to be enclosed by small spongioblastic cells, an arrangement imitating that of capsule cells. The entire pattern bore a conspicuous, if only superficial, resemblance to a spinal or a cranial nerve ganglion. Moreover, the giant cells, particularly the mononuclear forms, often bore a strong resemblance to ganglion cells.

The following phylogenetic factor may be invoked to explain this striking tendency to exhibit patterns of structures derived from the neural crest. In Acrania (Branchiostoma; Amphioxus) the primary sensory cells, with few exceptions, remain within the neural tube. The dorsal roots contain no spinal ganglia, and a neural crest is not present. In Petromyzon the neural crest and the spinal ganglia make their first appearance. However, in all fishes large primary sensory cells of the type of spinal ganglion cells are still present in the dorsal portion of the spinal cord. Even in amphibian larvae and reptilian embryos such elements still represent a transitory embryonic feature and are known as the transitory dorsal cells, or Rohon-Beard cells.

It may thus be assumed that the neural crest or the cells of the spinal and the cranial nerve ganglia represent alar elements which were originally enclosed within the neural tube and which secondarily migrated toward the periphery, possibly following a neurobiotactic stimulus, to aggregate as the neural crest and subsequent spinal and cranial ganglia (Kappers, 1920; Kuhlenbeck, 1927).

The nucleus of the mesencephalic root of the trigeminal nerve has thus been interpreted as a group of such primary sensory cells remaining in a phylogenetically primitive position within the neural tube.

As these ganglion-like neoplastic cell groups occur in neuroectodermal tumors within regions derived from the alar plate of the forebrain, it may easily be surmised that they have developed from embryonal cell remnants with primitive ganglionic crest potencies.

DISCUSSION

H. M. ZIMMERMAN (MC), U.S.N.R.: Dr. Globus' contention that the giant cells in malignant gliomas are neoplastic rather than inflammatory is not surprising to the general pathologist. The latter sees giant cells in other types of malignant neoplasms, such as the malignant melanoma, the chorioepithelioma and even certain carcinomas of the stomach. What is surprising is Dr. Globus' statement that the giant cells can and do break up into single nucleated glial tumor cells. It has generally been accepted, I believe, that multinucleated cells were the result of abnormal cellular division, or of cellular fusion, and thus represented a terminal state, or condition, of the cells. That such cells can divide to form single cells is a new idea.

DR. J. H. GLOBUS, New York: I believe the demonstration contains sufficient evidence in favor of cell division, rather than of cell coalescence, as a cause of giant cell formation.

Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain. DR. A. FERRARO, New York.

This paper was published in the December 1944 issue of the ARCHIVES, page 443.

Periarteritis Nodosa with Decerebrate Rigidity and Extensive Encephalomalacia in a Five Year Old Child. DR. N. MALAMUD, Ann Arbor, Mich.

The occurrence of periarteritis nodosa in childhood is not uncommon. But although there is considerable clinical evidence of involvement of the central nervous system in children with this disorder, there are few clinicopathologic reports in the literature, and, for this reason, the following case is presented.

REPORT OF A CASE

A 5 year old boy, while convalescing from an infection of the upper respiratory tract, had fleeting joint and abdominal pains. Examination revealed a systolic cardiac murmur, fever and leukocytosis, which led to a diagnosis of acute rheumatic fever. A week later, just as these symptoms began to subside, the patient suddenly had a series of convulsive seizures, became comatose and presented outspoken signs of complete decerebrate rigidity. The pupils were dilated and fixed to light, and there was mild papilledema. The temperature became elevated and irregular. Ventriculographic studies suggested a tumor of the brain stem. The patient's condition declined rapidly, and he died approximately two and a half months after the onset of the illness.

Necropsy revealed massive necrosis of the cerebrum. The entire cortex and the basal ganglia were spongy and friable, resembling milk curds, and were poorly demarcated from the somewhat firmer white matter. In Nissl preparations the necrotizing process could be traced down to the level of the red nucleus, where it stopped abruptly. Histologically there was noninflammatory, complete liquefaction necrosis of the tissue in a uniform stage of active gliomesodermal reaction. The brain stem and the spinal cord were intact, and there was only diffuse degeneration of Purkinje cells in the cerebellum. All the basal vessels were normal, but careful microscopic examination of the vessels in large sections revealed typical changes of periarteritis nodosa in the smaller meningeal arteries on the medial surfaces of the cerebral hemispheres. The disease was in a subacute phase, consisting in "hyaline" necrosis of the subintima and media, perivascular infiltration with lymphocytes and beginning fibrosis of the intima and adventitia, with narrowing of the lumen. Similar vascular lesions were present in the heart, resulting in anemic infarcts throughout the myocardium and a solitary aneurysm of the left marginal branch of the coronary artery. There were some lesions in the wall of the trachea, the gastrointestinal tract and the kidneys.

This case was unique in many ways. The clinical course was unusual in that only the brief initial symptoms were suggestive of periarteritis nodosa. These early signs were quickly obscured by a purely neurologic syndrome of decerebrate rigidity, so that a diagnosis of cerebral tumor was considered. There was a striking disproportion between the extensive destruction of the cerebral parenchyma and the restricted vascular lesions. This discrepancy has been observed by other authors, but probably only the case described by Baló was one of comparable severity. While periarteritis nodosa is admittedly a vascular disorder, this lack of parallelism between the vascular and the parenchymal involvement in some cases must be accounted for by other factors. Some authors attribute this to a toxic factor. In my opinion, the view recently substantiated experimentally by Rich and Gregory that periarteritis nodosa is an anaphylactic type of reaction is of interest in this connection. In the present case, the onset of the disease after an infection of the upper respiratory tract and its initial general effect on various tissues of the body, followed suddenly by an extensive necrotizing process in the brain, out of all proportion to the arteritis, suggest an allergic reaction.

DISCUSSION

DR. A. FERRARO, New York: The material presented by Dr. Malamud is of interest because it is in accord with the new concept of an allergic reaction of the brain in the presence of certain pathologic conditions. It is gratifying that he, too, has been thinking in such terms. Among such pathologic changes of particular interest is the periarteritis nodosa which he has described, and it is well known that such a condition is now considered the expression of an allergic reaction of the blood vessel walls. In view of this interpretation of the vascular damage, I agree with him that the rest of the pathologic picture can be viewed in the light of a more general allergic reaction of the brain tissue. I feel confident that the study of allergic reactions of the brain to various pathologic stimuli will open a bright new field for investigation and better understanding of brain pathology.

Cerebral Thromboangiitis Obliterans: Histogenesis of Early Lesions. DR. I. MARK SCHEINKER, Cincinnati.

This paper was published in full in the July 1944 issue of the ARCHIVES (**52**:27, 1944).

Neurogenic Polycythemia: Report of a Case. DR. A. EARL WALKER, Chicago.

Neurologic phenomena accompanying polycythemia vera are usually considered the result of the polycythemia, but a growing volume of literature has been accumulating suggesting that the cerebral lesions may be the primary factors in the production of the erythremia. Within the past four years I have performed operation in 2 cases of cerebellar hemangioblastoma associated with polycythemia, which disappeared after

removal of the tumor, and Dr. Henry Schwartz operated in a similar case. Two of these cases have previously been reported (Carpenter, G.; Schwartz, H., and Walker, A. E.: Neurogenic Polycythemia, *Ann. Int. Med.* **19**:470-481, 1943). A brief summary of the third case follows.

A. G. F., a machine operator aged 32, was admitted to the University of Chicago Clinics on Sept. 3, 1943, complaining of throbbing headaches of five months' duration. Except for erythematous papules on the face, physical examination gave normal results. Neurologic examination revealed only unsteadiness of gait. Examination of the blood showed a high erythrocyte count and elevation of hemoglobin but a normal white cell count, indicating that the erythrocytosis was not the result of dehydration. Spinal puncture revealed increased intracranial pressure (300 mm. of cerebrospinal fluid). Since ventriculographic study showed no dilatation of the cerebral ventricular system the patient was treated with phlebotomy, 1,000 cc. of blood being removed on two occasions. His condition, however, did not improve, although the degree of erythrocytosis decreased. On November 25 he was found to have papilledema; a second ventriculographic examination revealed symmetric internal hydrocephalus with anterior displacement of the aqueduct of Sylvius.

On November 30 the posterior fossa was exposed and a vascular tumor removed from the posterior part of the left hemisphere. The patient had an uneventful convalescence and was discharged to his home on the eighth postoperative day. Histologic study revealed that the neoplasm was a hemangioblastoma.

The plasma volume did not appreciably change after operation, although the red cell mass decreased almost 1 liter. This finding suggests that the condition was a real polycythemia, and not merely a hemoconcentration. It is true that the erythremia was never severe, but in view of the patient's weight the hematologic picture appears abnormal.

The presence of erythrocyte-regulatory centers in the diencephalon has been suggested by Schulhof and Mathies, da Rin and Costa, and Riccitelli, on experimental grounds. The clinical basis for such a hypothesis has recently been reviewed by Ferraro and Sherwood (*Psychiatric Quart.* **11**:19, 1937).

Apposite to this discussion is mention of the well controlled work of Schafer in production of erythremia, with a red cell count as high as 9,000,000 per cubic millimeter, in dogs by section of all afferent depressor fibers in the cervical region. The great increase in blood volume accompanying the polycythemia was shown to be due entirely to increase in the cell volume. Total sympathectomy abolished or prevented this effect. Hypertension with vasoconstriction is an essential part of the syndrome produced by section of the depressor fibers, and it is possible that the operation is nothing more than a surgical method of producing the type of polycythemia which Davis induced in man and animals with vasoconstrictor drugs. On the other hand, its implications with respect to possible erythrocyte-controlling centers cannot now be discounted.

In no instance of "neurogenic polycythemia" has there been described any notable enlargement of the spleen. This perhaps is in keeping with the concept of the erythremia as essentially symptomatic, it being widely held (though unproved) that splenic enlargement is due to the storage of cells unwanted by the circulation.

That the pathologic type of the tumor may have played an etiologic role in the polycythemia is not probable in view of the fact that in none of a series of 14 other cases of cerebellar hemangioblastoma was there any evidence of erythremia. Nor did Cushing and Bailey mention such a complicating condition in their review of the subject.

It is unlikely that an arteriovenous shunt in the cerebellum through the vascular tumor could be the cause of the polycythemia. Unfortunately, however, determinations of oxygen tension of venous and arterial blood for the head were not made, so that such a possibility cannot be entirely eliminated.

It may only be said at this time that polycythemia associated with cerebellar hemangioblastoma has been observed in 3 cases. The pathogenesis of the polycythemia must remain for further clinical and experimental studies to determine.

DISCUSSION

DR. L. ROIZIN, New York: Could the polycythemia noted in Dr. Walker's 2 cases be related to a neurohormonal mechanism? I ask this for the following reason:

In 1935, in collaboration with Dr. P. Foa (*Arch. di fisiol.* **35**:170, 1935), I investigated the influence of the central nervous system on the morphologic composition of the blood in dogs. In our experiments we studied the effects of the hydrodynamic changes in the spinal fluid pressure, the action of various vegetative-mimetic drugs and glandular preparations introduced into the cerebral ventricles and the influence of generalized convulsions produced by strychnine applied to the cortical motor region, followed by cutaneous stimulation of the area. Simultaneous registration of the blood pressure and oncographic study of the spleen and bone marrow (Tournade's method) revealed that increase in blood pressure and decrease in volume of the spleen were associated with erythrocytosis and leukocytosis (neutrophilia, lymphopenia and a shift to the left of Arneth's formula). In splenectomized dogs less pronounced erythrocytosis and slight leukopenia were noted. Variations in number of the white and the red blood cells also were observed in relation to emotional states in the animals. We concluded that the temporary increase of the white and the red blood cells was related to the stimulation of the neurovegetative centers of the diencephalon and medulla. Somewhat similar results were noted also by Borchardt in adrenalectomized cats and by Anderson and Witthower in human beings.

I wonder whether the polycythemia observed in Dr. Walker's cases before the operation and the return to normal afterward could be related to similar neurohormonal mechanisms elicited by abnormal pressure of the tumor or by hydrodynamic variations in the cerebrospinal fluid.

DR. H. M. ZIMMERMAN (MC), U.S.N.R.: Was there any evidence of hematopoiesis in the case of cerebellar hemangioblastoma?

DR. A. EARL WALKER, Chicago: The observations to which Dr. Roisin referred were disturbances of the entire hematopoietic system, which were not present in our cases of polycythemia associated with cerebellar hemangioblastoma. The erythremia in our cases was related to the red cell–forming mechanisms alone and probably is to be explained by a peripheral disturbance induced by the neuropathologic process. That intracranial hypertension alone produces polycythemia is not likely, since we were unable to find evidence of such a condition with other types of cerebral tumor associated with intracranial hypertension. The precise mechanism of the disorder must be left for further investigation.

Dr. Zimmerman asks whether there was any evidence of hematopoiesis. In these cases of symptomatic polycythemia, as is true in practically all such cases, there was no increase in the nucleated red cells. Unfortunately, biopsy of the bone marrow was not made in any of our cases, so that more direct evidence of increased hematopoiesis is not available.

Coagulation Necrosis in the Brain. DR. KARL T. NEUBUERGER, Denver.

This condition is more frequent than one would conclude from the literature. The anatomic picture exhibits the following main characteristics: more or less complete necrosis of the tissue; presence of doubly refractive, acicular "slits" (apparently the site of cholesterol crystals) and sometimes of amyloid bodies and extracellular lipid droplets; varying degrees of calcification (granules or fibrils), and absence of decomposition and organization inside the necrosis. The foci are sometimes present within softened tissue; they may become surrounded and replaced with collagen tissue, with islands of foam cells. Grossly, the foci are small, whitish and moderately firm.

The recent literature contains only a few related papers (Markiewicz; Ley; Credé). The material used in this study consisted of 18 cases, in which arteriosclerosis, trauma, neoplasm, embolism and meningitis were represented (slides).

The difference between this type of necrosis and liquefaction necrosis is evident. During only the earliest stages of an infarct in the brain is one unable to state in which direction the development will proceed. Coagulation necrosis differs also from caseation: An area of caseation is surrounded by specific granulation tissue; it is characterized by deposition of fibrinoid masses, preservation of elastic tissue and absence of slits. Coagulation necrosis in the brain has been compared to infarcts in the viscera (kidney and spleen). While such a comparison is partially justified, especially with regard to pathogenesis, it is not completely satisfactory. The fact that brain tissue undergoing necrosis is chemically different from visceral tissue should be considered. The brain is rich in cholesterol. Disintegration of the brain tissue, due to failing nutrition, sets free cholesterol esters; these substances are split, and cholesterol crystallizes, with formation of "slits." This process may be compared with what happens, for example, in atheromatous softening of the aorta. The breakdown may take place in areas of simple necrosis of brain tissue, or it may occur in tissue revivified by gitter cells.

The lesion is due apparently to complete ischemia of the region involved. In the cases examined, so far as could be determined, there was total or subtotal vascular occlusion. It is perhaps superfluous to bring in the term "fermental preparation" (*Aufbereitung*), as used by Markiewicz. He expressed the belief that such a preparation takes place in areas of ordinary softening under the influence of surrounding living tissue, which furnishes the ferments required; this preparation is said to be missing with coagulation necrosis. However, in softening of circulatory origin revivification arises not only from the surrounding tissue but from mesenchymal and glial tissues within the focus; one may assume that the nutritional supply is sufficient to maintain the reactability of the supporting tissue. It has been observed often that the center of a large infarct fails to become revivified and undergoes coagulation necrosis while the periphery displays the usual softening; in such cases there probably was an incomplete nutritional supply to the periphery, with total absence of such supply to the center. That a focus with early features of softening breaks down later and undergoes coagulation necrosis is due most likely to eventual deterioration of the nutritional supply.

DISCUSSION

DR. F. WERTHAM, Jamaica, N. Y.: Were the lesions of coagulation necrosis which Dr. Neubuerger described acute, or does he know of prestages out of which they developed?

DR. KARL T. NEUBUERGER, Denver: The lesions were either primary, with subacute to chronic development, or, in some instances, secondary, arising from preceding early stages of customary softening; this is indicated by the presence of occasional groups of gitter cells within the foci.

Lipoma in the Quadrigeminal Plate with Hydrocephalus: Report of a Case. DR. CHARLES DAVISON.

Lipoma of the central nervous system occurs chiefly in the region of the cisternal enlargements of the subarachnoid space and is closely attached to the meninges, the vessels or the nerves traversing the meninges. To date, about 80 cases of lipoma of the central nervous system have been reported. The superior surface of the corpus callosum and the tuber cinereum are the most common sites. In 8 cases of lipoma, including the present case, the site was the region of the quadrigeminal plate and around the trochlear nerve. In none of these cases, except Taubner's and mine, were symptoms noted. This neoplasm, which originates in the leptomeninges, a derivative of the neural crest, may grow along the nerves and vessels into the brain or the cord tissue and simulate infiltrative growths or give the impression that it actually arises from the neural elements. Frequently it compresses and distorts the nerve tissue. Most observers believe that the lipoblast which gives rise to the lipoma in the central nervous system originates from the mesenchyme, which, in turn, is a derivative of the ectoderm or the endoderm, arising apparently at the junction of these two germinal layers.

REPORT OF A CASE

A man aged 53, gainfully employed, had been born with a large head. A hopeless prognosis was made at birth. He did not attend school but was tutored up to the age of 14 years.

Examination disclosed symmetric enlargement of the calvaria, which measured 75 cm. in circumference. The left pupil was slightly larger than the right. Ocular movements were normal except for defect in convergence of the left eye. Air and bone conduction were diminished in the right ear. There was slight hyperreflexia in the left lower extremity. He was euphoric. Intelligence was about average. Toward the end of life, his ability to remember faces and names was poor.

At times he became noisy and complained of severe frontal headaches. During the last month there developed a subnormal temperature, which on several occasions dropped to 94 or 95 F. It persisted for one month, until his death.

Autopsy.—The lipoma extended from the inferior border of the superior colliculi to almost the lower limit of the fourth ventricle. The entire fourth nerve had disappeared except for a few partially demyelinated fibers, some of which were embedded in the tumor. The aqueduct of Sylvius was constricted, distorted and displaced practically throughout its length. There was

severe generalized hydrocephalus. The tumor was a typical lipoma.

DISCUSSION

H. M. ZIMMERMAN (MC), U.S.N.R.: I have observed 3 cases of intracranial lipoma in my necropsy material. In 2 cases the lipoma, which was asymptomatic, was situated in the quadrigeminal plate and was not associated with hydrocephalus. Dr. Harvey Cushing mentioned the first of these cases in his book on meningiomas. The third case was that of a lipoma in the region of the mamillary bodies. The tumor not only destroyed these structures but involved the mamillothalamic tracts. The patient had long-standing hyperthermia, of several years. The clinical and anatomic observations in this case were reported in the symposium on the Hypothalamus (*A. Research Nerv. & Ment. Dis., Proc.* [1939] **20**:824, 1940).

DR. F. WERTHAM, Jamaica, N. Y.: Were there lipomas of the skin in Dr. Davison's case? It is my impression that this lipoma is multiple, but from the data in reported cases I cannot draw a definite conclusion.

DR. CHARLES DAVISON: In my case there were no lipomas of the skin. In some cases multiple lipomas were present in the central nervous system and in other parts of the body.

Encephalitis Affecting the Basal Ganglia in Monkeys. DR. RICHARD RICHTER, Chicago.

The observations presented concern the pathologic observations on 2 monkeys (Macaca mulatta) with acute encephalitis of unknown cause. One of the animals had been inoculated two months before with suspensions of brain tissue from a patient who had died of chronic encephalitis, and the other had been subjected four months previously to bilateral temporal lobectomy. It was concluded, nevertheless, because of the long latent intervals between the experimental procedure and the onset of the acute cerebral disease, as well as for other reasons, that the terminal encephalitis was not due to the experimental factor, but was spontaneous in origin.

The principal lesions, which were of a necrotizing inflammatory type, were similar in the 2 animals and were strictly confined to the corpus striatum and the globus pallidus, but chiefly to the striatum. They were represented by bilateral focal, round areas of necrosis, sometimes confluent, which appeared, even grossly, as areas of "paling." In them no ganglion cells remained, but only a pale, structureless ground substance, within which were degenerated pyknotic glial nuclei and remnants of thickened, swollen blood vessels. In none of the lesions were there any fat granule cells or other evidence of release of fat; the lesions were not softenings but were foci or coagulation necrosis. At the borders of many of these lesions there were proliferation and hyperplasia of the neuroglia and perivascular and interstitial infiltrations of mesodermal inflammatory elements, in which polymorphonuclear leukocytes were prominent. Scattered, diffuse inflammatory changes of the microglia, with rod cell formation, were also observed at a distance from the necrobiotic areas in the caudate nucleus, the lenticular nucleus and the thalamus. In 1 of the animals foci of encephalitis, chiefly microglial, were present in the cerebral and cerebellar cortex; and in both monkeys there were inflammatory infiltrations of the meninges, slight in 1 animal but intense in the other. However, no destructive foci appeared in the cortex or elsewhere, except in the basal ganglia.

Occurrence of lesions of this type, with this localization, has not hitherto been reported in the monkey. Indeed, there are surprisingly few descriptions of spontaneous disease of the nervous system in primates. The reports that exist were reviewed briefly and the observations compared with the material present.

It is noteworthy that in 1 of these animals there developed rapid and extremely violent choreic movements which involved the trunk and the extremities, persisted for two days and then rapidly diminished. These were combined with severe ataxia, resembling that seen in Sydenham's chorea. Perhaps the greatest interest of this material attaches to the association of the chorea and destruction restricted to the basal ganglia, particularly to the corpus striatum. This, of course, corresponds to the accepted and frequently observed association of striatal damage with human chorea, but hitherto such a correlation has not been clearly observed in animals. Attempts to reproduce amyostatic syndromes in primates and other animals by ablation of or injury to the corpus striatum have been singularly fruitless, and there has been general agreement among almost all investigators since Kinnier Wilson that lesions confined to the striatum, even when large, fail to evoke noteworthy symptoms. Recently Fulton and Kennard, after inflicting unilateral and bilateral damage on the striatum of many primates, concluded that such lesions had no visible effect on motor performance when the nervous system was otherwise intact. They did, however, succeed in producing chorea in chimpanzees and monkeys in which ablation of cortical areas 4 or 6 were combined with bilateral destruction of the striatum. The results of ablation experiments are thus corroborated and extended by these observations on spontaneous striatal disease in monkeys. The material demonstrates, in addition, that chorea may appear in the monkey in the presence of basal ganglion disease alone, with an otherwise intact nervous system.

DISCUSSION

DR. A. WEIL, Chicago: Bilaterally symmetric necrosis of the corpus striatum of a monkey, similar to that which Dr. Richter demonstrated in his lantern slides, were produced by Crandall and Weil in a dog by ligation of the common bile ducts (Pathology of the Central Nervous System in Disease of the Liver, ARCH. NEUROL. & PSYCHIAT. **29**:1066 [May] 1933).

Were there any functional or histopathologic changes in the liver in this monkey?

DR. F. WERTHAM, Jamaica, N. Y.: I should like to ask Dr. Richter about the relation of the condition in his animals to the spontaneous diseases in monkeys described by Bodechtel and Scherer.

DR. RICHARD RICHTER, Chicago: In answer to Dr. Wertham's question, Bodechtel described a spontaneous disease in a monkey which was characterized by mild meningeal infiltrations, retrogressive changes in the ganglion cells and pronounced perivascular infiltration of lymphocytes and plasma cells, together with the glial reaction, which consisted especially in proliferation of rod cells. While these changes were qualitatively similar in some respects to the lesions in my monkeys, the localization was quite different, since it was chiefly in the cortex and there was a little inflammatory reaction in the basal ganglia or elsewhere in the nervous system. A somewhat similar inflammatory condition appearing spontaneously in a larger group of monkeys was reported by van Bogaert and Scherer, in which necrobiotic changes, combined with an intense glial and mesodermal inflammatory reaction, were present in the cerebral cortex, particularly that of the occipital lobes. This group of monkeys exhibited blindness, ataxia and convulsions, and in none of them was there any involve-

ment of the basal ganglia. In another report Scherer described disseminated demyelinating lesions deep in the cerebral hemispheres and in the white matter of the spinal cord of monkeys which became ill in epidemic fashions. The disease in these animals had nothing in common with the condition which I have described.

In answer to Dr. Weil's question, the liver of the first monkey presented no noteworthy changes on microscopic examination. There was no opportunity to study the liver of the second animal.

Histologic Changes in a Case of Paramyoclonus Multiplex. DR. GEORGE B. HASSIN, Chicago, and DR. RICHARD KEPNER, Honolulu, Hawaii (by invitation).

Pathologic observations in cases of motor restlessness, described in 1881 by Friedreich as paramyoclonus multiplex, are rare, while the cause and localization of the lightning-like muscular contractions, usually devoid of synchronism and symmetry, are on the whole not known. They have been looked for in vain in the central and peripheral nervous systems and in the muscles themselves. More successful were studies on the type of paramyoclonus which is associated with epilepsy—the so-called epileptic myoclonia, or myoclonus epilepsy. In cases of this form, cerebral changes have been demonstrated in the nerve cells in the form of cytoplasmic inclusions, so well described recently by Ferraro and Roisin (*J. Neuropath. & Exper. Neurol.* **1**:297, 1942). Unfortunately, the muscles were not studied by these investigators.

A generous supply of muscle tissue was obtained for biopsy from an elderly psychotic woman who for years had been an inmate of the Territorial Hospital in Honolulu. For about ten years she had exhibited involuntary contractions in various muscles of the upper and lower extremities and the neck. The contractions would disappear for two or three months and then recur with the same vigor. The specimens of muscle, which were stained with hematoxylin and eosin and by Van Gieson's method, exhibited for the most part normal muscle fibers, of normal size and possessing normal striations. In some muscles the Cohnheim fields were disrupted, and vacuoles were present, while the sarcolemma, the endomysium and the walls of the blood vessels showed nuclear hyperplasia. In general, the parenchymatous changes, though present, were mild and were much less in evidence than the mesodermal changes. Neither type of lesion, however, was commensurate with the severity of the clinical manifestations and differed greatly from the lesions seen in cases of Landry's paralysis, amyotonia congenita and progressive muscular dystrophy. They were probably secondary to, or the result of, muscular hyperactivity of many years' duration. Muscular hyperactivity may result, for instance, in hypertrophy of the muscle fibers, as was stated by Ramsay Hunt in 1903. In a subsequent contribution, however, he expressed the opinion that the hypertrophy was the result of hyperactivity, that is, was secondary. The causative process of paramyoclonus multiplex is thus most likely a lesion in the central nervous system, such as produces the epileptic myoclonia of Unverricht and Lundborg. The Friedreich and the Unverricht-Lundborg type are evidently one disease process, a peculiar form of epilepsy, of which the Friedreich type is the incomplete form. Electroencephalographic and other studies would be of great interest in the investigation of these two forms of paramyoclonus multiplex, as well as of a third form, classified as hysterical.

Book Reviews

Symptoms of Visceral Disease: A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, A.M., M.D., LL.D., F.A.C.P. Sixth edition. Cloth. Price, $5. Pp. 442, with 87 illustrations in text and 10 color plates. St. Louis: C. V. Mosby Company, 1944.

The subtitle of Pottenger's book is its best description. It is concerned with psychosomatic medicine in the strict sense. The author's background—he is a specialist in diseases of the chest—led him to the subject in an attempt to discover why one disease causes different symptoms in different patients. He finds much of the answer in analysis of the many factors involved in production of symptoms. These factors include a multiplicity of visceral reflexes with individual thresholds, relative sympathicotonia and parasympathicotonia, ionic intracellular differences and hypersensitivity phenomena. The principal emphasis is placed on the vegetative nervous system, which determines the division of the book into four parts: the introduction; the vegetative nervous system; its relationship to symptoms of visceral disease; and the innervation of important viscera, with the study of viscerogenic reflexes.

Pottenger's point of view is unitarian: His orientation is to the patient rather than to the disease. That he has succeeded in his chief goals is attested by the fact that the present edition is the sixth; on the other hand, one wishes that he might have incorporated more new material.

The content, which is factual and detailed, does not allow for easy reading. For subsequent editions one would suggest summaries at chapter ends wherever possible. There is a dearth of newer references in the anatomic and physiologic sections, with few, if any, later than 1937; the great majority are far earlier.

The book is of unquestionable value to the internist, as well as to the neurologist and the psychiatrist. It covers a field too often neglected by persons who should be most familiar with it. The book is highly recommended.

An Introduction to Physical Methods of Treatment in Psychiatry. By William Sargant and Eliot Slater. Price, 8s, 6d. Pp. 171. Edinburgh: E. and S. Livingstone, Ltd., 1944.

This book, according to the authors, was written primarily for the student, the young psychiatric clinician, the general practitioner and the psychiatric nurse. The central aim is to present certain of the physical therapeutic methods used in psychiatry with regard to indications, technics, advantages, disadvantages and results. Under discussion are the various insulin technics, metrazol and electric convulsion therapy, the drugs used in treatment of epilepsy, the various sedative and stimulant drugs, the role of diet, vitamins and endocrine preparations, the malarial treatment of dementia paralytica, and, finally, prefrontal leukotomy. All this material is handled objectively, and, while the tone in general is perhaps slightly optimistic, no glowing claims are made for any one procedure.

The chief discussion and criticism of the book will probably come in relation to the emphasis on the so-called constitutional approach. This is expounded in the "Introduction," which is preceded by the following quotation from Henry Maudsley, dated 1870. "The observation and classification of mental disorders have been so exclusively psychological that we have not sincerely realized the fact that they illustrate the same pathological principles as other diseases, are produced in the same way, and must be investigated in the same spirit of positive research. Until this be done, I see no hope of improvement in our knowledge of them, and no use in multiplying books about them."

While the authors in general ascribe to the concept of multicauses, the psychosomatic approach, treatment of the patient as a whole, etc., they lay great emphasis on the so-called genetic potentiality, with the omnipotent genes exerting their specific effects at different developmental periods. Thus, "Inherited tendencies to dementia praecox, involutional melancholia, and to senile dementia lie hidden through the years to manifest themselves in due course when the appropriate time comes." Similar tendencies to anxiety, worry, obsessional thinking and hysterical phenomena are described.

The authors, further, are of the school that believes that everything can, and eventually must, be explained in physiologic terms. Psychologic differences are, therefore, finally to be explained in terms of altered physiologic function.

The book would seem to be of value in relation to its objective presentation, in a brief volume, of a set of physical therapeutic methods in psychiatry. Its theoretic aspects are dogmatically stated with a goal of simplicity, and at the usual cost.

Spina Bifida and Cranium Bifidum. By Franc Ingraham. Pp. 216, with illustrations. Cambridge, Mass.: Harvard University Press, 1944.

This is a bound collection of five reprints which appeared in the *New England Journal of Medicine*. It gives an account of the numerous cases of meningocele, spina bifida and allied conditions which have been observed at the Children's Hospital over many years, analyzed in modern terms. The author's operative methods, indications and results are presented.

Particularly interesting is the description of a series of 20 cases of the Arnold-Chiari malformation. The author recommends operation in cases in which the general neurologic condition is good, though he is not optimistic as to the results.

All in all, the papers present a creditable report on a long term investigation, which is still in progress.

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STUDIES ON PAIN

"SPREAD OF PAIN"; EVIDENCE ON SITE OF SPREAD WITHIN THE NEURAXIS OF EFFECTS OF PAINFUL STIMULATION

BRONSON S. RAY, M.D., AND HAROLD G. WOLFF, M.D.

NEW YORK

The crossed extension reflex shows that noxious stimuli can cause a spread of excitation that involves adjacent segments on the same and on the opposite side of the cord. Further, it has been suspected from the spread of deep pain from visceral disease that similar spread of excitation involving adjacent segments of the cord might occur. However, as far as can be ascertained, it has never been demonstrated that such spread involving sensation occurs at the segmental, rather than at a suprasegmental, level.[1]

The following data are evidence as to the site of occurrence in the neuraxis of the spread of excitatory processes from deep painful stimulation of high intensity.

CLINICAL DATA

F. W., a lawyer aged 48, had been found in 1940 to have a papilloma of the bladder, causing hematuria. The lesion was treated endoscopically by fulguration. With a recurrence of symptoms, he was admitted for the first time to the New York Hospital on March 20, 1944, where Dr. Allister McLellan performed a biopsy and fulguration of a papilloma of the bladder (presumably recurrent). The pathologic report was that of a transitional cell carcinoma. Because of persistent hematuria a suprapubic resection of the bladder was performed by Dr. McLellan on April 4.

Shortly after this operation the patient consulted Dr. Lewis Stevenson because of pain in the right hip and buttock, extending into the right lower limb as far as the foot. The limb also became progressively weaker, making weight bearing impossible. By July 1944 pain and weakness in the right buttock and the right lower lim were of such a degree that the patient was confined to bed and required occasional opiates. He did not complain of pain anywhere on the left side. The evidence indicated metastatic tumor involving the right hip joint and the right pelvic nerve plexus.

Roentgenotherapy failed to reduce the intensity of the pain; therefore, on Aug. 21 a chordotomy (section of the ventrolateral portion of the cord) was performed by Dr. Ray at the first thoracic segment on the left side only.

Examination on September 6 revealed that all pain sense (including deep pain perception) was lost below the nipple line on the right side to within 1 cm. of the midline. Temperature sense was lost in the same region. There was no demonstrable impairment of touch sense. The plantar responses were flexor in type, and there was no clonus. Sphincter function was normal. There was no sensory change on the left side.

After the operation the patient was free of all pain on the right side, but under certain circumstances he

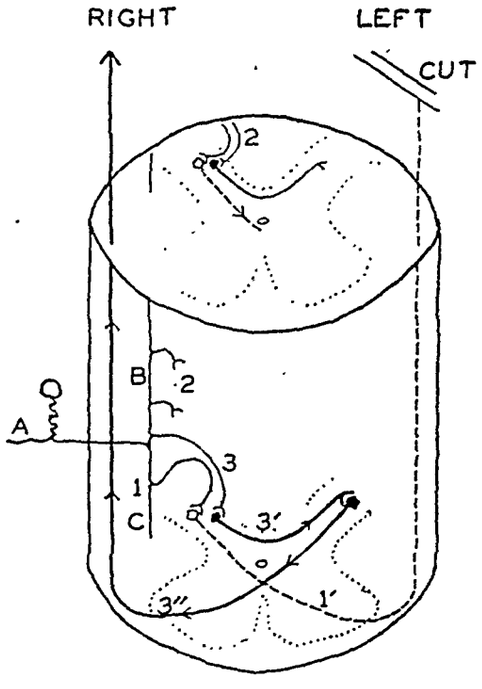

Fig. 1.—Schematic representation of the pathways for the "spread of pain" within the spinal cord. *A* represents primary sensory neuron, dorsal root ganglion; *B*, ascending branch of the sensory radicle, and *C*, descending branch of the sensory radicle. *1* is a collateral to the posterior horn of the nearest spinal segment. This connects with neuron *1'* which crosses to ascend in the opposite spinothalamic tract. *2* indicates collaterals to the adjacent segment, and *3*, collaterals to the posterior horn connecting with neuron *3'*, which forms part of the posterior commissure in crossing to the opposite posterior horn, where it arborizes to connect with neuron *3''*; this, in turn, crosses back to ascend the cord in the spinothalamic tract on the side of entry of the noxious impulses.

In patients F. W. and W. O. the spinothalamic tract was cut on the left side, and therefore the impulses from noxious stimulation ascended to the suprasegmental structures only on the right side.

From the New York Hospital and the Departments of Surgery, Medicine (Neurology) and Psychiatry, Cornell University Medical College.

1. Wolff, H. G.: Some Observations on Pain, in Harvey Lectures, 1943-1944, Lancaster, Pa., Science Press, 1944, pp. 39-95.

experienced pain in the left buttock and, to a lesser degree, in the left heel. He reported that deep pressure over the trochanter and movement of the right hip induced pain on the left side.

Examination on September 9 revealed that when the position of the right lower limb was changed so as to move the diseased right hip or when heavy pressure was made over the trochanter of the right femur, the patient complained of pain of moderate intensity in the region of the left hip and buttock. He placed the palm and extended fingers of his left hand over the lateral portion of the left buttock to indicate the site and distribution of his pain. It was conceivable that moving the right limb stretched or displaced structures on the left side to produce pain. To resolve this doubt, the calf muscles on the right (diseased) side, far from the metastatic extensions, were vigorously squeezed in such manner as would produce intense deep pain in a normally innervated structure. No pain was experienced in the right calf, but a deep, aching pain was felt diffusely up and down the left leg as high as the hip, especially in the calf and heel. Similarly, vigorously squeezing the muscles on the right flank induced a diffuse ache over the left flank and the left side of the abdomen.

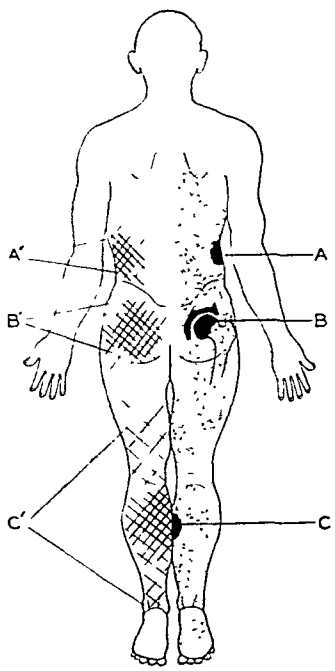

Fig. 2.—Schematic presentation of the analgesia and spread of pain in patient F. W. The stippled area shows the area of analgesia following chordotomy on the left side, approximately at the first thoracic segment. *A*, *B* and *C* are sites of noxious stimulation of high intensity on the analgesic side. *A'*, *B'* and *C'* are the diffuse areas of pain of low intensity perceived when areas *A*, *B* and *C* respectively were stimulated.

The following observations were made, the most intense pain being graded as 10 plus:

1. Deep pain of 6 to 8 plus intensity induced by compressing muscle in the left lower limb or on the left (normal) side of the abdomen did not induce pain anywhere on the right side.

2. Deep pain induced on the left (normal) side by movement of or deep pressure on the right (diseased) hip joint or by squeezing the right gastrocnemius muscle was only of 1 or 2 plus intensity and began about a half-second after the beginning of the noxious stimulation. The pain was diffuse, poorly localized and widespread. Also, it outlasted the period of stimulation by about half a second.

3. Stimulation, such as gentle rubbing of or pressure on the skin of the right (diseased) leg produced no pain on the left side. Only on deep noxious stimulation of the right (diseased) leg was pain perceived on the left side.

4. Noxious stimulation of the right leg and thigh (diseased side) by repeated pinprick did not induce pain sensation on either the right or the left side. The effects of noxious stimulation in producing burning sensation were not tested.

5. Noxious stimulation of low intensity, of the right (diseased) leg did not induce pain on the left side.

Comment.—The deep pain induced on the left side through movement of the diseased right hip did not result from secondary contractions of muscles of the left leg or buttock. With noxious stimulation of the nondiseased parts of the right leg, such as the gastrocnemius muscle, or the muscles of the abdomen and flank, pain was also experienced in corresponding areas on the left side.

Non-noxious stimulation of shorter or longer duration, such as gentle rubbing of or pressure on the skin and muscle of the right (diseased) leg produced no pain on the left side. Therefore the perception of deep pain in the left (normal) limb from noxious stimulation of the right limb could not have been due to the facilitating effects of non-noxious stimulation from the right side enhancing the perception of subthreshold noxious stimuli from the left side.

From a study of the following case similar observations on deep pain were made; in addition, it was possible to obtain data on cutaneous pain.

W. O., a linotype operator aged 41, was first admitted to the New York Hospital in April 1943, complaining of pain in the left side of his face and neck of about seven years' duration. Surgical exploration revealed a cholesteatoma at the base of the skull and in the region of the foramen magnum; the growth was removed. At the time of operation a small amount of the cholesterol crystal contents of the tumor escaped into the subarachnoid space.

The first of a series of readmissions to the hospital was in July 1943. The patient complained of almost continuous burning and aching pain in the sacrum and buttocks, which radiated down the posterior and lateral aspects of the thighs and legs into the ankles and toes. The pain during the ensuing year became worse on the right side than on the left. An exploratory laminectomy, in August 1943, had revealed radiculitis and arachnoiditis in the region of the cauda equina associated with aseptic meningitis. As a result of intrathecal injections of alcohol the patient had cutaneous hypalgesia of the foot and lower part of the leg on the right side.

By October 1944 the pain in the right leg had become unbearable and intractable, and a chordotomy at the first thoracic level, with section of the ventrolateral

region of the cord on the left side, was performed by Dr. Ray. After operation there was a defect in pain and temperature perception on the right side as high as the third thoracic segment, the site being slightly higher for temperature and slightly lower for pinprick. The patient felt no more spontaneous pain in his right leg, nor did he perceive pinprick, deep pain or heat or cold in this leg. However, when the gastrocnemius muscle was vigorously squeezed on the right (analgesic) side, he felt a diffuse, aching pain on the medial aspect of the thigh adjacent to the scrotum on the left (control) side. A metal tube containing hot water at a temperature of 80 to 90 C. applied to the skin just above the right knee was felt as burning pain in the left groin (control side). Also, heat applied to the right (analgesic) side of the abdomen was felt as burning pain on the left (control) side of the abdomen. The intensity and duration of stimulation necessary to produce this phenomenon were sufficiently great to result in diffuse reddening of the skin at the site of application.

Ice, when pressed against the skin for thirty to sixty seconds in the same areas, similarly induced on the left side a sensation of "burning" cold. All forms of noxious stimulation when applied to the left, or control, side elicited pain more promptly and of greater intensity than when applied to the right side and were identical in time and intensity with that described for F. W. Stimuli from warm and cold tubes at temperatures of 45 to 50 and 15 to 20 C. respectively, and from pinprick on the right (analgesic) side were not perceived on the left (control) side. Application of intense heat below the right knee produced no sensation on the left (control) side. About one week after the chordotomy the pain on the left side, which had been minimal at the time of admission, became progressively more intense.

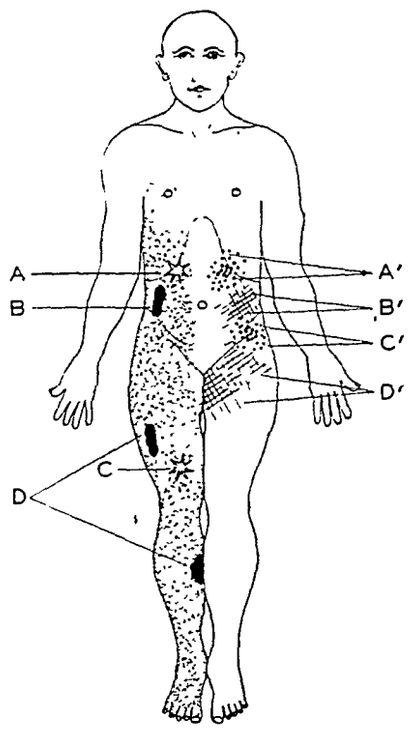

Fig. 3.—Schematic presentation of the analgesia and spread of pain in patient W. O. The stippled area shows the area of analgesia following chordotomy on the left side, approximately at the first thoracic level. *A* and *C* are sites of noxious stimulation of high intensity with heat (80 to 90 C.) on the analgesic side; *A′* and *C′* are the diffuse areas of burning pain of low intensity perceived when areas *A* and *C* respectively were stimulated; *B* and *D* are sites of noxious stimulation of high intensity with vigorous squeezing of muscle on the analgesic side, and *B′* and *D′* are the diffuse areas of aching pain of low intensity perceived when areas *B* and *D* respectively were stimulated.

Comment.—These considerations support the contention that excitation from noxious stimulation of high intensity spreads at the segmental level in the spinal cord. There it gives rise to effects which involve neurons in adjacent segments, as well as neurons that connect with the opposite side of the cord. Impulses are then conveyed headward through the intact spinothalamic tract and ultimately result in pain sensation.

The spread of pain after unilateral chordotomy from the diseased side to the side with normal sensation has been noted before in this clinic, but demonstration of the nature of this spread has been unsatisfactory because of the complicated illnesses of the patients in whom it was seen. Observations closely resembling those on F. W. and W. O. have been made on 2 other patients, but the patients whose cases are described here were especially astute and cooperative witnesses.

INTERSEGMENTAL AND INTRASEGMENTAL CONNECTIONS: POSTULATED PATHWAYS FOR "SPREAD OF PAIN"

Many collaterals of the sensory radicals conducting impulses from noxious stimuli, after entering the cord, terminate in the gray matter of the posterior horn close to the point of entry and come into synaptic relation with neurons the axons of which cross in the anterior commissure and ascend in the spinothalamic tract on the opposite side of the chord. Collaterals arising from the ascending branches of the sensory radicles connect with neurons in the substance of Rolando, other parts of the posterior horn and the central and intermediate gray matter. They terminate in the gray matter of segments of the cord adjacent to those of their entry.[2]

Furthermore, arising from the ascending and descending branches of the sensory radicle is another important group of collaterals. These collaterals establish synaptic relations in the dorsal horn with internuncial neurons the axons of which form the most dorsal part of the posterior commissure. At their terminations these axons ramify about cells in the dorsal horn on the opposite side of the cord. It may be accepted as a general principle that the collaterals of sensory radicles do not cross directly to the opposite

2. Ramón y Cajal, S.: Histology, Baltimore, William Wood & Company, 1933.

side of the cord.[3] The two sides are connected by means of internuncial neurons. Such internuncial chains supplement the shortest path for noxious stimuli to the suprasegmental structure. Moreover, if there is sufficient background of facilitation, together with sufficient intensity of stimulation, these less direct internuncial chains undoubtedly become passable.[4]

It is postulated from the observations on patients that there is a spread of excitation from the primary sensory neurons and their collaterals so as to involve (1) neurons in the segments of the cord of their entry and in adjacent segments that cross to the opposite side and ascend the cord in the spinothalamic tract, and (2) internuncial neurons that cross in the posterior commissure to stimulate neurons on the opposite side of the cord. The latter cross back to ascend the cord in the spinothalamic tract on the same side as the entering noxious impulses.

Each additional synapse introduced by internuncial neurons increases the resistance to the spread of excitation. Hence, it is conceivable that one or more intercalated neurons necessary for the passage of impulses from the side of entry to the other side of the cord introduce resistance which makes high intensity of noxious stimulation necessary for the spread of pain to the opposite side of the body.

Patient W. O. experienced pain before chordotomy from roots giving rise to both deep (aching) and superficial (burning) pain. These pains were far more intense on the right side but were present to a minimal degree on the left. After chordotomy burning and aching pains became more intense on the left side.

Before chordotomy patient F. W. experienced deep pain originating in the right, or abnormal, lower limb, but this was not associated with pain on the left, or normal, side. Several possible explanations suggest themselves: (1) The pain from the diseased (right) side was of such high intensity that the patient failed to perceive lesser pain on the opposite side; (2) section of the ventrolateral part of the cord on the left side, by removing suprasegmental inhibitory systems, altered the excitability of neurons in the cord and facilitated transmission at heretofore resistant synapses, and (3) spread of afferent impulses to the opposite side of the cord occurred as much before as after section of the spinothalamic tract, but with both spinothalamic pathways in operation there was interference with further transmission, which prevented these impulses from giving rise to sensation.

3. Lorente de Nó, R.: Personal communication to the authors.

4. Lorente de Nó, R.: Analysis of the Activity of the Chains of Internuncial Neurons, J. Neurophysiol. **1**:207 (May) 1938.

GENERAL COMMENT

Instances of spread of pain from deep noxious stimulation have been described and discussed elsewhere.[5] Suffice it to say here that this phenomenon results from spread of excitation within the cord, that such spread of excitation is mainly on the side of primary noxious stimulation, that direction of spread is somewhat more cephalad than caudal and that it does not equally involve all segments over which it spreads. Also, when the intensity of noxious stimulation is great, the opposite side may become involved.

From experimental evidence reported elsewhere [1] it has been inferred that surface "hyperalgesia" associated with deep noxious stimulation and pain, and perhaps some types of deep "hyperalgesia," result from reenforcement occurring within the cerebral cortex.

It is suggested therefore (1) that "hyperalgesia" and "hyperesthesia" associated with deep pain result from a modification within the cerebral cortex of the normal threshold surface impulses so that they seemingly are more intense and of longer duration; (2) that localization, true and false, involves conditioning or previous experience, and therefore functions of the cerebral cortex, and (3) that phenomena referable to segments of the cord account for the spread of the sensory and the motor effects associated with cutaneous burning, noxious impulses and pain of visceral origin.

THERAPEUTIC IMPLICATIONS

When a patient with intractable unilateral pain of high intensity is subjected to unilateral chordotomy the possibility exists that after the operation he will experience pain on the heretofore normal side. Unilateral chordotomy carries with it less hazard of serious damage to the cord than bilateral chordotomy; there is less likelihood of impairment of sphincter control, and, in the case of high cervical chordotomy, less danger to the respiratory mechanism is involved. For the relief of unilateral pain of low or moderate intensity by

5. McAuliffe, G. W.; Goodell, H., and Wolff, H. G.: Experimental Studies on Headache: Pain from the Nasal and Paranasal Structures, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:185, 1943. McLellan, A. M., and Goodell, H.: Pain from the Bladder, Ureter and Kidney Pelvis, ibid. **23**:252, 1943. Kunkle, E. C.; Goodell, H., and Wolff, H. G.: Observations on the "Ice Cream" Headache, unpublished data; cited by Wolff.[1]

chordotomy unilateral section is adequate and preferable, but for the relief of unilateral pain of high intensity bilateral section is superior to the unilateral operation.

SUMMARY AND CONCLUSIONS

Patients with hemianalgesia following high thoracic section of the ventrolateral portion of the cord on one side perceived pain on the normally innervated side of the body when the analgesic side was noxiously and intensely stimulated. Pain was not perceived on the analgesic side when the normally innervated side was noxiously stimulated.

It is inferred from these observations that the spread of pain of high intensity from one part of the body to adjacent regions on the same side and on the opposite side is a sequel of the spread of excitatory processes within the neural segments of the cord. Such spread of excitation via the neurons in the dorsal horns and the association pathways then incites impulses on the same and on the opposite side of the cord, some of which ascend the spinal cord to the suprasegmental structures, where neural function is ultimately expressed in the perception of pain. In short, the postulated spread of excitatory processes associated with pain of high intensity primarily involves the segmental structures, although secondarily the suprasegmental structures are implicated in perception, localization and reaction.

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EDEMA AND TROPHIC DISTURBANCES OF THE LOWER EXTREMITIES COMPLICATING PREFRONTAL LOBOTOMY

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Since April 1, 1942, 19 patients of the Milwaukee Sanitarium have had bilateral prefrontal lobotomies. All operations were done by two skilled and experienced neurosurgeons, who used the lateral approach described by Freeman and Watts.[1] Two of the older patients died of pneumonia while convalescing from the operation. Still another had acute collapse of a lung soon after the lobotomy but recovered. The very first patient to undergo the operation has since had one convulsion, but is regularly employed. None of the others, to our knowledge, has had convulsions. Immediately after operation all had rectal and vesical incontinence. Ten of the 17 survivors continue to have occasional sphincter accidents. One patient had a short, but intense, bout of diabetes insipidus during recovery from the procedure, but the complication was quickly controlled with posterior pituitary injection U. S. P.

In the course of our postoperative observations on these 17 patients, 8 have presented complications referable to the legs and feet. Six have had bilateral edema, in 4 of whom the edema was associated with tenderness. In 2 patients a tendency to edema of the feet and legs existed before the operation but was much aggravated after it; moreover, in these 2 patients bullae developed about the heels at points most vulnerable to pressure. After the operation 1 patient observed that her feet were swollen and required shoes a size larger. In another patient bullae developed on the heels but there was no edema.

It would seem that the incidence of these complications was greater than could be accounted for by mere chance. However, because the disturbances are usually mild and tend to pass away within a few months, they have doubtless often been overlooked. In a recent extensive review of the international literature on psychosurgery, Walker[2] did not report any cases of such complications. Freeman and Watts, in their many publications in this field, apparently have not discussed them.

Edema of the lower extremities is not particularly unusual among patients with mental disorders. It is more likely to be found in persons who are inactive, remaining in one position for long periods. It is not uncommon in elderly patients. We have also seen edema of the legs in men and women with mental disorders who were normally active and in whom it was indeed difficult to determine the cause. Obregia and associates[3] and de Giacomo[4] discussed some aspects of this subject.

For the most part, the patients in the present study were too ill to cooperate adequately in neurologic examination. There is much that one would like to know about some of them, especially whether the sensory system was disturbed. On April 1, 1944 Kindwall and Cleveland[5] completed a follow-up study on 15 of the surviving patients and have described elsewhere in detail the clinical effects of the operation. Some essential facts about the 8 patients with complications involving the lower extremities are given in the following clinical sketches. These cases are presented in the order of severity of the sequelae, complications in case 1 being the most disabling and distressing and those in case 8 the least so.

REPORT OF CASES

CASE 1.—F. M., a woman aged 53, who was divorced, had been a musician. She had progressed in school to junior college. Since the age of 20 she had been mentally ill more than half the time and had been in sanatoriums continuously since the age of 34. In 1929 she was examined at the Mayo Clinic, where, in addition to the psychosis, she was observed to have edema and cyanosis of the hands. Her psychosis had two

From the Milwaukee Sanitarium.
† Dr. Ziegler died on Jan. 8, 1945.

1. Freeman, W., and Watts, J. W.: Psychosurgery, Springfield, Ill., Charles C Thomas, Publisher, 1942.

2. Walker, E. A.: Psychosurgery: Collective Review, Internat. Abstr. Surg. **78**:1-11, 1944.

3 Obregia, A.; Dimolescu, A., and Sulica, M.: Physiopathogenesis of Acrosyndromes in Psychopathic Patients, Cluj. med. **15**:265-268 (May 1) 1934.

4. de Giacomo, U.: Su significanto di manifestazioni edematose osservate in olienati degenti negli ospedali psichiatrici, Riv. sper. di freniat. **61**:1090-1094 (Dec. 31) 1937.

5. Kindwall, J. A., and Cleveland, D.: Prefrontal Lobotomy: Fifteen Patients Before and After Operation, Am. J. Psychiat., to be published.

phases, which lasted a few days each and alternated more or less regularly. In one phase she was impulsive and yelled loudly, was profane, and sometimes obscene, and her remarks were critical and sneering. In the other phase she was fearful, acted as though hallucinated and withdrew entirely from others but was quiet. She did little work with her hands but read newspapers and listened to music over the radio. She had been given no shock therapy. Except for slight edema of the feet, physical and laboratory examinations revealed essentially a normal condition, and she had good control of the sphincters at all times. Her gait was normal.

Prefrontal lobotomy was performed on Sept. 19, 1943, and the cut was extended the following day. Pronounced incontinence of the bladder and rectum followed, and she has continued to soil herself occasionally since. Soon after the operation pronounced edema was observed in her lower extremities, extending nearly to the knees. The edematous areas were dry, pale and warm and did not pit easily; her feet were extremely tender. Soon after large bullae appeared on the backs of her heels, seemingly the result of pressure. Despite every precaution, such as elevation of the feet and relief from pressure, the bullae broke down and the resultant ulcers healed slowly; they resembled trophic ulcers in every way. Her toes assumed awkward positions and underwent rhythmic movements of an athetoid nature. For eight months she refused to walk and screamed whenever her legs or feet were touched. The edema and tenderness gradually subsided, and the ulcers healed. The accompanying photograph, taken May 1, 1944, shows the greatly improved condition of the extremities. On that date the ankle jerk was elicited, but not the knee jerk. Sensation seemed intact. The feet continued to be tender. Since May 1 she has been walking some and worn shoes. The psychosis has changed somewhat, but on the whole she has not improved. She remains in the sanatorium.

Fig. 1.—F. M.'s extremities as of May 1, 1944, more than seven months after lobotomy, when the edema had largely subsided, the ulcers on the heels had healed and she was beginning to walk, with help.

Case 2.—E. S., a very large man aged 44, married, had never had a regular occupation. He reached about the third year in college. At the age of 28 he began to have erratic and unstable behavior and was probably hallucinated. Since then he has been in many sanatoriums. He has expressed delusions, and occasionally what the "voices" have told him has sent him into a rage. He stared, held fixed positions and masturbated excessively. A course of insulin shock produced only temporary improvement. Slight edema of the feet and ankles had been present prior to the operation. At times he had soiled himself with urine. Some tremor of the thumb and the index finger had been noted. Except for these disturbances, physical and laboratory examinations revealed an essentially normal condition.

Lobotomy was performed on Jan. 11, 1944 and was completed four days later. After the operation the patient had an acute collapse of the lung. Marked incontinence appeared immediately, and he has continued to soil himself occasionally since. Soon after the operation pronounced edema of the lower extremities was observed. The edematous areas were pale, warm and dry, did not pit easily and were not tender. Within three weeks after the operation small bullae, seemingly due to pressure, appeared on the heels; they persisted from one to two months but did not ulcerate. Except for sluggishness, he walked without difficulty. After operation he showed a grasping reflex in both hands, which persists in mild form. The tendon reflexes were present. A Babinski sign was occasionally elicited in the left foot. The tremor persisted. Sensation appeared to be intact.

At the time of writing, seven months after lobotomy, the edema of his feet persists. He speaks only an occasional word but smiles at jokes and seems relaxed. Initiative is returning slowly. There have been no angry outbursts at the "voices," but he has admitted hearing them. He remains in the sanatorium.

Case 3.—R. M. R., a teacher aged 48, single, was graduated from college with Phi Beta Kappa honors. In early girlhood she became a worrier. Soon after the death of her father, when she was 35, she began to accuse herself of many things that were untrue. She worried over an unconsummated love affair and had fears which she could not understand. Since that time she has been in one sanatorium after another. Her spells of worry gave way to long periods of silence and uncommunicativeness, during which she stared and smiled; these spells were interrupted by short periods of excitement, in which she talked and listened to voices. In these excitements she was often noisy and sometimes combative, talked in an abusive, profane, surly manner and appeared on the point of frenzy. At the age of 41 she had edema of the ankles, which a salt-free diet dispelled. A full course of insulin shock therapy caused a gain in weight but gave only transitory improvement. At night she occasionally soiled herself with urine. Physical and laboratory examinations revealed an essentially normal condition.

Lobotomy was performed on Feb. 7, 1944, and the section was extended on March 9, 1944. Immediately after the first operation the patient was incontinent, and this has persisted, with occasional recurrences. Soon after the operation her left hand was observed to be edematous; this was attributed to intravenous medication or to her lying on it. Several weeks after the operation her feet were observed to be edematous, the left being more affected than the right. The

edematous areas were pale, dry and warm and pitted easily. At present her feet are very tender to pinprick or tickle. She limps a little on her left foot. In a neurologic examination, done on July 1, 1944, a slight grasping reflex was observed in both hands. She did not use the left hand as well as the right and did not swing her left arm much in walking, although muscular power in it appeared to be normal. The knee and ankle jerks were present. There were no signs of lesions of the pyramidal tract. The tissues of the left hand and forearm had a different texture from those of the right, feeling slightly more indurated.

The edema persists but responds to elevation of the extremities involved. The patient is still in the sanatorium in an inactive, quiet state, staring and smiling to herself. Unless provoked, she has no periods of excitement, and she adjusts herself better in a social group and requires less care.

CASE 4.—M. J., a single woman aged 32, a college graduate and a teacher of Romance languages, had an insidious onset of the illness at the age of 21. By the time she was 26 she had lost interest in her surroundings, was aloof, easily offended, expressed bizarre ideas and had a pronounced energy defect. She often smiled to herself and at times told of the voices she heard. She was sometimes angry and combative, and it became necessary to place her under custody in a state hospital. Insulin and metrazol shock treatment produced improvement, which, however, did not endure. Her hands and feet were often cyanotic and cold. She had never soiled herself. Physical and laboratory examinations revealed an essentially normal condition.

Lobotomy was performed on Sept. 14, 1943. After the operation the patient had pronounced incontinence, which has since recurred at infrequent intervals. Soon after the operation her feet and legs, halfway to her knees, had a warm, pink edematous appearance, which lasted two to three months. During this time she walked as though her feet were tender and cried out in distress when slight pressure was applied to the ankles. Neurologic examination gave otherwise normal objective results.

Since the operation she is not aloof, laughs easily and is more sociable; however, at times she gets very angry. She must be urged to write letters or work in the occupational therapy room. She remains in the sanatorium.

CASE 5.—F. L., a woman aged 42, had a private finishing school education. As a child she was "very good" but shy and tense. She married at the age of 23, had one child and was divorced several years later. At about the age of 30 she began to withdraw, even from her nearest relatives, and became careless about her personal appearance. At that time she expressed fears without being able to tell what made her afraid. Wherever she might be she would scream; in a store or restaurant she sometimes became disturbed and talked in a loud, accusing manner. At times she remained in bed all day. Before 1940 she had been in sanatoriums for brief periods; since that time she has been in an institution continuously. She stared, held fixed positions, smiled to herself and had occasional noisy outbursts of anger. She spoke little, was stilted in behavior and showed a pronounced energy defect. Full courses of insulin and metrazol shock therapy produced only transitory improvement. Although she sat about in fixed positions a great deal, she had no edema of the legs. She soiled herself at times. Except for secondary anemia and a moderate degree of undernourishment, physical examination and laboratory studies revealed an essentially normal condition.

Lobotomy was done on Feb. 22, 1944. Severe bleeding was encountered. Soon after the operation diabetes insipidus appeared, and the patient drank several quarts of water a day; this condition was controlled with posterior pituitary injection and has subsided. Immediately after the operation there was considerable incontinence, which soon decreased in severity but has continued to occur at intervals. Soon after the operation the feet and legs were slightly edematous for about three months and appeared dry, pale and tender. After the operation the patient became more animated and less completely preoccupied; her behavior, however, remains stilted. On the other hand, she does more things without being urged, and there have been fewer spontaneous outbursts of anger and irritability. She continues to live in the sanatorium.

CASE 6.—K. M., a married woman aged 44, a high school graduate, began to show personality changes at the age of 40, when fatigue and depression caused her to resort to the excessive use of alcohol. She described feelings of unreality and inertia. Electric shock always dispelled these feelings and produced a hypomanic state; relapse, however, took place within a few weeks. Insulin shock only caused a gain in weight. She had an old ankylosis of the left hip joint. At no time in her life had she had trouble with sphincter control. Aside from the ankylosis of the hip, physical examination and laboratory studies revealed an essentially normal condition.

Lobotomy was performed on Nov. 3, 1943. Five days later the operation was extended. Incontinence largely subsided in one to two months but recurred occasionally for six months. Slight edema of the legs was observed soon after the operation; this disappeared within two to three months and caused no distress. The results of neurologic examination were normal while the edema was present. After the operation the patient became mildly elated, but not to such a degree as she had after electric shock therapy. She has retained this state and is getting on reasonably well at home save that, aside from pressure of speech, she lacks energy.

CASE 7.—V. R., a single woman aged 28, completed three years of high school and attempted to become a clerk; she tried other occupations, as well, but fatigue prevented sustained work. At the age of 15 she began to be obsessed with her own tensions. She was jealous of her parents. Suicidal ideas were expressed many times. She often paced the floor at night saying, "I can't stand it." She had had no trouble with sphincter control. There was evidence of old thrombophlebitis in the left leg. Electric shock treatment gave only temporary relief. Mild insulin shock therapy only caused her to gain weight. Except for the thrombophlebitis, physical examination and laboratory studies gave essentially normal results.

Lobotomy was done on Jan. 28, 1944. Convalescence from operation was uneventful, and before the patient left the hospital the sphincters were under control. She wrote letters home three weeks after the operation. She noticed that her feet were swollen after the operation, and she was obliged to use shoes one size larger. Her feet were not tender. Neurologic examination gave normal objective results. She is now cheerful, easy-going and lacking in ambition but gets on at home with urging and guidance.

CASE 8.—G. E., a high school boy of 16, was said to have presented a difficult feeding problem in infancy and may have been born prematurely. At the age of 14 he lost interest in school and was unable to do simple chores at home. These disabilities increased. Later, he talked to himself, twirled a lock of his hair most of the day and repeated the same remarks many times. Even his mother called him "silly," as he muttered in a low monotone, expressing bizarre ideas. Insulin and

electric shock treatments had little effect. He was undernourished, although he ate and slept well. Physical examination and laboratory studies revealed an otherwise normal condition.

Lobotomy was done on Jan. 14. 1944. The patient regained complete control of his sphincters within a month after the operation. Some bullae appeared on his heels. Neurologic examination gave normal objective results. He gained weight rapidly. At the time of this report his energy not only is greatly increased but is directed toward wider interests. He is making mediocre progress in a boarding school and is happy. No evidence of a psychosis is apparent.

The word "edema" derives from the Greek word οἴδημα, which means "swelling." It has come to have a special connotation, implying swelling due to excess water or fluid in the spaces between the tissue cells. In this it differs from the Latin word "tumor," which also means "swelling," but implies an overgrowth of tissue.

The simplest mechanism for the production of edema is a direct trauma to the tissues. Generalized edema is seen in the acute stages of infection, such as trichinosis. When the globulin-albumin ratio of the blood serum becomes too disordered, edema is likely to result. Damaged kidneys may be rendered unable to prevent albumin from passing into the urine; this favors the production of edema. Partial or complete circulatory obstruction, such as may occur in the veins of the leg, produces edema. Edema occurs also with cardiac failure, but not in every case. It is often seen after serious damage to the liver. Edema may be found in association with general starvation (cachexia) and is one of the commonest symptoms of vitamin B deficiency, as manifested in beriberi. Mild edema is seen at times with other forms of peripheral neuritis. A peculiar type of edema, which is called myxedema, appears in some patients with hypothyroidism. Lymphatic obstruction, too, causes an unusual type of edema known as lymphedema, commonly seen with elephantiasis. Although Quincke,[6] in 1882, and others before him, had described acute circumscribed edema, Strübing,[7] in 1885, first gave it the name angioneuritic edema, thus implying its relation to the nervous system and the blood vessels. Osler[8] first pointed out the hereditary tendencies of angioneurotic edema, which is said to occur intracranially on rare occasions. Urticarias are frequently related to allergy. A menstrual edema has been described. In 1892 Milroy[9] described an unusual form of edema of the lower extremities. He had observed it in families, the hereditary character indicating that some particular quality of the tissues predisposed to its occurrence.

These suggestions from clinical medicine point to elemental or primary factors in the pathogenesis of edema, among which should be mentioned (1) change in the permeability of damaged capillary walls; (2) changes in capillary pressure; (3) variations in the colloids of the blood serum; (4) lymphatic obstruction; (5) unknown hereditary factors, and (6) disturbances in central or peripheral innervation. Because of the nature of the complications under discussion, the possible relations between function of the nervous system and edema deserve further consideration.

The Peripheral Nervous System.—No work on this part of the nervous system has been more important than the pioneer demonstrations of Claude Bernard, who, in 1851, proved that the sympathetic nervous system subserves the function of vasoconstriction. Since his time many workers have shown the vasodilator and sweat-inhibiting effects of severing the sympathetic nerves from the central nervous system. One might conclude that after lumbar sympathectomy standing would increase the volume of the legs. (Standing has this effect in normal, healthy persons.) However, inconclusive evidence presented by Gambill, Hines and Adson[10] from a study of 4 patients about twenty days after lumbar sympathectomy for hypertension indicated that the standing volume of the legs was less after the operation than before.

The Central Nervous System.—For many years evidence has accumulated to suggest that the brain, and perhaps the brain stem and the spinal cord, may play a part in the production of edema. In 1867 Chevallier[11] wrote a thesis for the faculty in Paris on paralysis of vasomotor nerves in hemiplegia. In 1876 Eulenberg and Landois[12] came to the conclusion that there were

6. Quincke, H. I.: Ueber akutes umschriebenes Hautödem, Monatsh. f. prakt. Dermat **1**:129-131, 1882.

7. Strübing, P.: Ueber acutes (angioneurotisches) Oedem, Ztschr. f. klin. Med. **9**:381-389, 1885.

8. Osler, W.: Hereditary Angioneurotic Edema, Am. J. M. Sc. **95**:362-367, 1888.

9. Milroy, W. F.: An Undescribed Variety of Hereditary Oedema, New York M. J. **56**:505-508, 1892; Chronic Hereditary Edema: Milroy's Disease, J. A. M. A. **91**:1172-1175 (Oct. 20) 1928.

10. Gambill, E. E.; Hines, E. A., and Adson, A. W.: The Circulation in Man in Certain Postures Before and After Extensive Sympathectomy for Essential Hypertension, Am. Heart J. **27**:360-380, 1944.

11. Chevallier, P. E.: De la paralysie des nerfs vasomoteurs dans l'hémiplégie, Thesis, Paris, no. 175, 1867.

12. Eulenberg, A., and Landois, L.: Ueber die thermischen Wirkungen experimenteller Eingriffe am Nervensystem und ihre Beziehung zu den Gefässnerven, Virchows Arch. f. path. Anat. **68**:245-271 and 489, 1876.

centers in the cerebral cortex near the motor centers for the arm and leg which influenced the vascular state of the extremities. In 1888 Gowers [13] reported similar observations, including the occasional presence of subcutaneous edema of the paralyzed part as a result of cortical or capsular lesions. In 1899 Parhon and Goldstein [14] studied 86 hemiplegic patients, 8 of whom had edema of the paralyzed hand. These authors did not attribute it to inactivity but stated that it was more probably related to hemianesthesia. Whenever edema has been found in association with hemiplegia it has usually been in the upper extremity. That edema and lesions of the central nervous system could be definitely related was suggested by Stone,[15] who, in 1929, reported his observations in the unusual case of a young girl who had had hemiedema with hemiplegia due to cerebral softening from embolus. Although he was unable definitely to locate an "edema center," after careful study of the patient's brain, his case, perhaps as much as any other reported up to that time, has helped to demonstrate a factor in edema referable to the central nervous system. In 1934 Kennard [16] presented experimental evidence for vasomotor representation in the cerebral cortex of monkeys. In 1935 Bucy [17] reviewed the literature and reported the clinical observations in an unusual case in which outspoken vasomotor changes were associated with paralysis of cerebral origin. In 1936 Luhan [18] found evidence of hemiedema in 15 of 100 cases of hemiplegia selected at random. In 7 cases, he gave detailed findings, including observations at necropsy in 2 of them. In his summary he said:

> . . . The cerebral lesion effects a tendency to localize actual or potential edema to the paretic extremities. . . . thus far the results of clinical studies which were checked with postmortem observations have not furnished any critical evidence for a cerebral vasomotor center of contralateral dominion.

In a summary and review of the literature in 1944 Kennard [19] accumulated additional clinical data from human subjects and brought together the experimental observations, including those of Fulton [20] and others, bearing on vasomotor representation in the cerebral cortex. The results of extirpation and stimulation experiments on monkeys and other animals have not been constant, and conclusions are difficult to draw. In general, it seems that area 6 (Brodmann) in monkeys contains within it elements capable of affecting the vasomotor system and the temperature of the contralateral extremities. This autonomic representation may extend somewhat into areas 4 and 8. The area for the leg is just anterior to the cortical motor centers for the leg and foot; the area for the arm, anterior to the cortical motor centers for the hand and arm.

The floor of the fourth ventricle, the brain stem and the hypothalamus have been shown experimentally to have an influence on the vasomotor system. Whether these areas are parts of association pathways or relay centers is not clear. Perhaps on the basis of such inconclusive evidence, Freeman and Watts [21] suggested that cutting the fasciculus cinguli might contribute to incontinence, in view of interruption of possible pathways between the cortex and the hypothalamus.

The motor cortex representing the foot appears to be a narrow zone anterior to the central sulcus, and at the very vertex of the hemisphere. The central sulcus is usually visible on the mesial surface of the hemisphere. About it on the mesial surface is the paracentral lobule, said to contain cortical sensory and motor representation for rectal, vesical and sexual structures. Green and Oldberg [22] and Erickson [23] have recently reported on patients with lesions of the paracentral lobule and adjacent structures and have reviewed pertinent literature bearing on it. The cortical center for the foot and the paracentral lobule are in close proximity. The rectogenitovesical structures themselves and part of the feet receive their innervation (sensory and motor) via centers in the sacral portion of the spinal cord. As might be expected, cortical

13. Gowers, W. R.: A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1905, vol. 2.

14. Parhon, C., and Goldstein, M.: Contributiui la studiul contracturiei in hemiplegia, Romania med. **7**: 2-12, 1899.

15. Stone, T. T.: Hemiplegia with Hemiedema Due to Cerebral Softening, J. Nerv. & Ment. Dis. **69**: 651-660, 1929.

16. Kennard, M. A.: Vasomotor Representation in Cerebral Cortex, Science **79**:348-349, 1934.

17. Bucy, P. C.: Vasomotor Changes Associated with Paralysis of Cerebral Origin, Arch. Neurol. & Psychiat. **33**:30-52 (Jan.) 1935.

18. Luhan, J. A.: Hemiedema in Cases of Hemiplegia, Arch. Neurol. & Psychiat. **36**:42-56 (July) 1936.

19. Kennard, M. A.: The Precentral Motor Cortex, in Bucy, P. C.: Autonomic Functions, chap. 11, to be published.

20. Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, Arch. Neurol. & Psychiat. **31**:221-235 (Feb.) 1934.

21. Freeman, W., and Watts, J. W.: The Frontal Lobes and Consciousness of the Self, Psychosom. Med. **3**:111-119, 1941.

22. Green, J. R., and Oldberg, E.: Injuries of the Vertex of the Skull with Special Reference to the Paracentral Lobules of the Brain, Arch. Neurol. & Psychiat. **53**:89 (Jan.) 1945.

23. Erickson, T. C.: Erotomania (Nymphomania) as an Expression of Cortical Epileptiform Discharge, Arch. Neurol. & Psychiat. **53**:226 (March) 1945.

representations for such sacral neurons, so diverse in function, are very near each other.

In order to visualize the part of the cerebrum affected by the lobotomy, we went to the anatomic laboratory and cut through a brain in the plane of the lobotomy. On a sketch of the cut surface (fig. 2) we outlined the fields of the two chief operative approaches. The cut is presumed to be made in the white matter anterior to the premotor (extrapyramidal) cortex, near the plane of the coronal sutures.

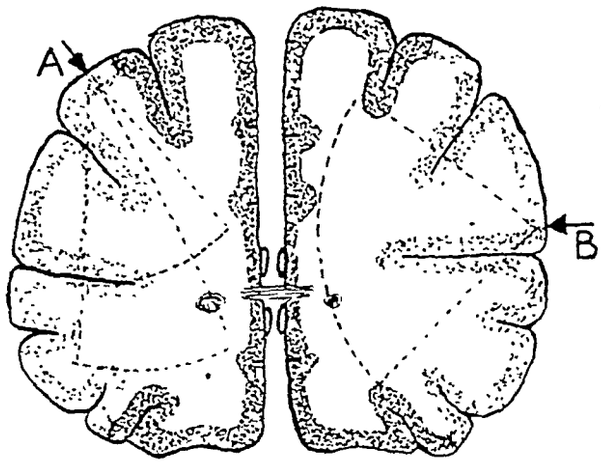

Fig. 2.—Drawing of the coronal surface of the brain at the plane of lobotomy. A few fibers of the most anterior portion of the corpus callosum are shown, with the tip of the anterior horn of the lateral ventricle at either side. The portion of the cortex which is shaded darker is that supplied by the anterior cerebral arteries, which are shown cut across below and above the corpus callosum. *A*, indicates the superior operative approach and the outline of areas which may be cut; *B*, the lateral operative approach and the outline of the area which may be cut.

From figure 2 the impression is gained that numerous association tracts, variable in length, including the frontothalamic, may be sectioned to some degree by the operation. The more specific nature and function of these tracts offer a fertile opportunity for investigation. If one may assume that man has cortical vasomotor representation in area 6, some of the fibers passing from such cells to the internal capsule may be injured directly by the lobotomy even when it is made fairly far anterior. From the position of these supposed vegetative centers, however, it might be assumed that more trophic disturbance would result directly from the lobotomy cut if it were made farther posterior. We have collected data that bear on this point.

At the time of operation it is customary for the surgeon to inject iodized poppyseed oil 40 per cent into the lobotomy cut and make a roentgenogram of the head to ascertain the plane of the lobotomy. This was done for all 17 of our patients. We have studied these roentgenograms and have classified the planes of the cut as anterior to, under, just posterior to or considerably posterior to, the plane of the coronal sutures. These data, together with those on the complications, including the persistence of incontinence, are presented in the accompanying table.

Correlation of Location of Lobotomy Cut (with Regard to Plane of Coronal Sutures) with Duration of Incontinence and Complications in the Extremities

Case No.	Plane of Iodized Oil in Lobotomy Cut as Seen in Roentgenograms of Skull in Relation to Plane of Coronal Sutures				Complications		
	Anterior	Under	Slightly Posterior	Considerably Posterior	Incontinence Lasting Less Than a Month	Incontinence Persisting Several Months	Extremities
1 F. M.	..	+	..	..	..	+	Severe tenderness and edema of legs and feet; bullae on heels
2 E. S.	..	..	..	+	..	+	Marked edema of legs and feet; bullae on heels
3 R. M. R.	..	..	..	+	..	+	Moderate tenderness and edema of feet; edema of left hand
4 M. J.	..	..	+	..	..	+	Mild tenderness and edema of legs and feet
5 F. L.	..	..	+	..	..	+	Mild tenderness and edema of feet
6 K. M.	..	+	..	..	..	+	Mild edema of legs
7 V. R.	..	+	..	..	+	..	Swelling of feet
8 G. E.	..	+	..	..	+	..	Bullae of heels
9 T. E.	..	+	..	..	+	..	None
10 S. M.	..	..	+	..	..	+	None
11 K. H.	..	+	..	..	+	..	None
12 L. W.	..	+	..	..	+	..	None
13 P. K.	+	..	..	..	+	..	None
14 T. O.	..	+	..	..	..	+	None
15 K. E.	+	..	..	..	+	..	None
16 L. E.	..	+	..	..	..	+	None *
17 B. M.	..	..	..	+	..	+	None *

* This patient had preoperative edema of the legs and feet, which disappeared after the operation because of increased activity (?) or trophic changes (?).

Of the 8 patients with complications referable to the legs, 6 had occasional incontinence of the bladder and rectum for considerably more than a month after the operation. Of 9 patients without complications of this sort, only 4 had such prolonged incontinence. Therefore it appears that complications in the legs may have something in common with persisting incontinence. However, the suggestion that the more posterior sections may be associated with such complications is not

entirely sustained by the data in the table. The lobotomy in case 17 was carried rather far posterior. Although the patient had persisting incontinence, at no time after the operation did she have edema of the legs. In fact, a slight preoperative edema of the legs disappeared subsequent to the operation. The lobotomy cut in case 1 was not posterior, and yet of all the patients she had the severest complications in the legs and persisting incontinence. There is, nevertheless, evidence in the table that the more anterior lobotomy is likely to be attended with less incontinence. These disconcerting facts, whatever their explanation may be, cause one to surmise that there may be anomalies of brain structure. The shape of the skull, too, may reveal discrepant relations between exterior landmarks and brain structure. The blood supply of the brain may be anomalous. There may be vasomotor representation in the cortex of a dual and antagonistic nature which overlaps considerably in one hemisphere. There may also be bihemispheral overlapping of function. Such possibilities could well account for the discrepancies in the results of experimental investigations on animals.

One must ever bear in mind the teaching of Hughlings Jackson that very different symptoms are to be expected from destruction than from stimulation of the nerve tissue. Alteration of the vascular supply of the brain may impair the functional integrity of structures at a considerable distance from the vascular defect. The portion of the cerebrum nourished by the anterior cerebral artery serves well to illustrate this point. This artery courses backward [24] over the mesial surface of the brain, sending branches laterally, upward and posteriorly to supply the gray and white matter of a narrow volume of the cerebrum adjacent to the mesial surface as far back as the parieto-occipital sulcus. Some branches of the anterior cerebral artery are said to supply the anterior portion of the thalamus, the basal ganglia and a part of the internal capsule. From a study of figure 2 it can be seen that small branches of the anterior cerebral artery might suffer interruption by the lobotomy, with consequent damage (small infarcts [?]), perhaps with mixed stimulating and destructive effects. Such possible infarcts might conceivably damage cortical association fibers, and even the cortex itself. The areas most vulnerable would be the uppermost portion of Brodmann's areas 8, 6 and 4, the paracentral lobule and mesial cortex anterior to it and sensory cortex representing the foot posterior to the central sulcus.

Necropsy studies are needed to clarify some of these questions. Plethysmographic observations on the legs before and after operation would doubtless give helpful information. If the operation were done on one side at a time, the intact side might serve as a control for the effects of operation. The anterior cerebral artery and its possible anomalies deserve renewed investigation. There are so many anomalies of the brain and skull that it would seem wise in dealing with the latter to remove a larger bone flap in preparation for the lobotomy, at present generally done through small openings in the skull.

We have not satisfactorily explained the clinical complications in the lower extremities in cases of prefrontal lobotomy. However, bedside observations on man and experimental investigations on monkeys point to areas in the brain lesions of which may produce edema and vascular and trophic disturbances. A more careful analysis in man of the functions of the cerebral cortex and subcortical structures nourished by the anterior cerebral artery may contribute greatly to the understanding of this problem. Milroy's disease (familial hereditary edema) and other obscure edemas of the feet and legs, as well as bullae, may be found to have a causative factor in the central nervous system, and it may well be discovered that enuresis is more than a defective habit, important as that can be.

The Milwaukee Sanitarium.

24. For charts of the blood supply of the brain, see Ranson's "Anatomy of the Nervous System" and Cunningham's "Text-Book of Anatomy."

ORGANIC PSYCHOTIC SYNDROMES OCCURRING DURING ELECTRIC CONVULSIVE THERAPY

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In electric convulsive therapy the first clinical improvement is frequently followed by an acute psychotic picture which is an organic reaction caused by the treatment. Not only are such disturbances of practical importance for the correct application of electric convulsive therapy, but they have many theoretic implications of great interest. The much discussed impairment of memory is the most constant, but never the only, organic mental symptom during electric convulsive therapy. Careful examination will reveal equally early symptoms in the emotional sphere. In a fair number of patients more dramatic syndromes develop. These always have certain characteristic features which permit their diagnosis as organic psychotic reactions implanted on the psychosis for which the patient is being treated; they disappear within one or two weeks after the last treatment. Their misinterpretation often leads to untimely cessation of treatment or, more frequently, to its unnecessary prolongation because of symptoms which are mistaken for residual manifestations of the patient's original illness.

Their symptoms repeat the great variety of acute syndromes occurring as organic reaction types. Early the patients show difficulty in concentration, have various physical complaints and manifest what has been called "organic neurasthenia." All intellectual functions, grasp as well as memory and critical faculty, are impaired; fatigability, circumstantiality and tendency to perseveration become obvious. Later, Korsakoff-like pictures may develop. The patient is disoriented in space and time, is incoherent in speech and action and shows aphasic-apraxic symptoms. Associations become poor. Often, disturbances of affect dominate the picture. Some patients become euphoric; others, fearful; still others go from bewilderment to a severe furor. Patients in psychomotor excitement aggravated by delusional fears and hallucinations make senseless attempts to escape, trying to go through windows and disregarding injuries. A typical delirium is not infrequent. Patients who never had hallucinations have vivid hallucinatory experiences. They experience entire scenes, which are changeable and may stir their fear to a panic. When treatment is continued in spite of such productive symptoms, these manifestations usually are replaced by a simple dementia. At this stage the patient may wet and soil himself, wander around aimlessly or become underactive and pass into a vegetating existence.

It is common to all these manifestations that they clear up one or two weeks after the last treatment; even the most dramatic symptoms often disappear suddenly on the fifth or sixth day. There is always complete amnesia for these syndromes even if the content of the pretreatment psychosis is well remembered.

Sometimes patients who had reached a quiet state of dementia recover by going again through a productive phase, with disturbed behavior, assaultiveness, delusional fears and hallucinations.

A. C., aged 18, with dementia precox, catatonic type, and no history of hallucinations, received twenty electric convulsion treatments. He became free from symptoms after four treatments but later showed an organic type of reaction, which finally resulted in a state of quiet, silly confusion. Five days after the last treatment he became acutely disturbed, had a hunted look, accused himself of being a murderer and saw preparations for his execution. An interview revealed the organic type of these symptoms, which were accompanied by complete disorientation. No further treatment was given, and five days later full recovery took place.

The correct interpretation of these late manifestations of an organic reaction is of special importance, for if they are mistaken for a relapse of the original psychosis they may lead to unnecessary reinstitution of treatment.

A few of the organic mental symptoms may be discussed in more detail. The impairment of memory follows the pattern seen in all organic diseases of the brain and extends gradually from more recent to remote recollections. This is well exemplified by a patient who was born in Russia, lived for many years in Germany and has been

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Some observations mentioned in this paper were made by the author at the Pilgrim State Hospital, Brentwood, N. Y.; director, Dr. Harry J. Worthing.

in this country for fifteen years. He first lost his English and was able to speak only German. After more treatments he spoke only Russian, without realizing that nobody understood him. After treatment had been discontinued, ability to speak the languages returned in the same sequence. The condition of this rather unproductive patient, with paranoid schizophrenia, who also went through an acute hallucinosis during the treatment, has now been in full remission for two years, without showing any memory difficulties.

The disorientation of these patients involves not only time and place but also person. They do not realize their defect and improvise explanations, but are not productive in confabulations. When the organic episode has cleared up, it becomes obvious that no actual loss has occurred. Therefore, when intense treatment is necessary to achieve results,[1] the occurrence of an organic reaction is no reason that treatment should be discontinued for fear of mental sequelae. Psychologic studies have confirmed the opinion that no actual loss of memory is demonstrable in patients after a course of electric convulsive therapy.[2] The learning ability in particular was found unimpaired. A physician suffering from a depression and showing a Korsakoff picture during the treatment was able, a few months later, to pass a difficult examination.

A case especially rich in its organic symptoms may be described briefly.

D. B., a woman aged 20, a quiet hebephrenic patient, without delusions or hallucinations, went through the first nine treatments uneventfully, with only slight confusion. After the tenth treatment she began to hallucinate, showed signs of psychomotor agitation and talked incessantly and incoherently. A sample of her uninterrupted productions follows: "Tonight I saw little satans on the door, but God was awfully nice to me. I wanted to go to bed with Tommy. I had Germans here tonight killing me. I am awfully sexually inclined. The Germans were shooting at me, but I beat them all up. I do read the Bible. I saw many seraphims on the door." After two more treatments she became quiet, stood around, looked silly and embarrassed and talked hardly at all. Four days after the twentieth, and last, treatment this stuporous condition began to disappear. She looked fearful, cried and again, two days later, became acutely disturbed; she would dance, sing, tear her clothes, roll over the floor, bite other patients, soil and smear. During the following day the picture was exactly that shown during the actual treatment, which was characterized by visual hallucinations and uninhibited sexuality. Again, two days later, i. e., nine days after the last treatment, she was perfectly quiet, well behaved, oriented and reasonable.

It is common experience in electric convulsive therapy that the clinical improvement occurs during the first five treatments. When new psychotic symptoms appear during the subsequent convulsions, they are usually signs of an organic reaction. They often show features reminiscent of the illness suffered by the patient prior to treatment; thus, a patient with a manic-depressive psychosis is more likely to show an organic reaction with affective tainting, and a schizophrenic patient, more schizophrenia-like symptoms. However, a differential diagnosis of the original psychosis and the organic reaction occurring during the treatment is usually possible: In schizophrenic patients the occurrence during electric convulsive therapy of cloudiness, disorientation, affective incontinence and efforts on the part of the patient to establish a better contact with the physician will suggest the diagnosis of an organic reaction. The hallucinations of an organic reaction are more vivid, and often changing, and the patient's affective response to them is stronger than is usual in schizophrenia. Apparent changes from a quiet hebephrenic state to one of acute excitement, or from a catatonic stupor to a productive paranoid state, with hallucinations and delusions, is generally a transient organic reaction. Permanent transitions from one subtype of schizophrenia to another are rare and were not seen in any of my patients receiving shock therapy.

The recognition of an organic reaction in patients with manic-depressive psychoses is sometimes more difficult. A depressed patient who has been free from symptoms after four treatments may become apprehensive or worried about physical complaints after a few more treatments. Simultaneous signs of a slight confusion and the different type of depression, characterized by a more superficial fearfulness, reveal the organic reaction. Therefore, it would be a mistake to continue treatment with the expectation of recovery from this reaction, which will clear up spontaneously when treatment is discontinued. The often mentioned "hypomanic reaction" after treatment of a depression is usually a transitory organic syndrome, characterized by silly euphoria and great suggestibility. On the other hand, a manic patient treated twice, two years apart, showed on both occasions a short organic reaction of depressive tainting. True shifting from one phase of the manic-depressive psychosis to the other was seen only in patients who had shown such alternation prior to treatment.

1. Kalinowsky, L. B.: Electric Convulsive Therapy, with Emphasis on Importance of Adequate Treatment, Arch. Neurol. & Psychiat. **50**:652 (Dec.) 1943.

2. Zubin, J., and Barrera, S. E.: Effect of Electric Convulsive Therapy on Memory, Proc. Soc. Exper. Biol. & Med. **48**:596, 1941. Sherman, I.; Mergener, J., and Levitin, D.: The Effect of Convulsive Treatment on Memory, Am. J. Psychiat. **98**:401, 1941.

A predisposition to psychotic reactions of organic type can be assumed. In cases of symptomatic psychoses occurring during infectious and toxic diseases, the presence of such a predisposition was assumed from observations that the same patient reacted to repeated infections each time with a psychosis. During electric convulsive therapy, although all the patients have some organic symptoms, the degree varies considerably; and in several instances both the intensity of the reaction and the type of symptoms remained the same during different courses of treatment. One patient with three courses of therapy reacted each time with a severe Korsakoff syndrome after as few as four treatments. Several patients with two long courses of therapy showed a surprising scarcity of organic symptoms during each course. Although such experiences make the existence of predisposing factors probable, none could be defined except that patients in the involutional period of life seem to become more confused. Very old patients, in whom arteriosclerotic or senile changes in the brain could be expected, showed surprisingly little organic reaction, although their confusion after each individual treatment was longer than that in younger patients. There is no relation between the intensity of the organic reaction described here and that of the confusion after each individual convulsion which was discussed in other reports.[3] There is no evidence that psychotic patients are more susceptible to organic mental symptoms than neurotic patients. Aside from the impression that catatonic patients especially often failed to show organic signs, no relation between the degree of severity of organic symptoms and the type of disease could be established.

The organic psychotic syndromes during electric convulsive therapy offer almost experimental conditions for studies on "pathoplastic" influences of various factors on the structure of a psychosis.[4] Thus, the type of symptoms in psychoneurotic patients is usually in accordance with their schizoid or cyclothymic personality traits. It is equally understandable that psychotic patients show organic reaction types with affective or schizophrenic features in accordance with their original mental illness. Exceptions to this rule are of particular interest: One schizophrenic patient in two series of treatments showed the same depressive-hypochondriacal reaction, followed by a manic-euphoric picture; she was of pyknic type, had some affective symptoms, and in the beginning her illness had been diagnosed as a manic-depressive psychosis by several psychiatrists. Another exception was a patient of pyknic type with clearcut catatonia who after fifteen treatments showed a manic-like organic reaction with grandiose ideas. The influence of constitutional factors was equally well demonstrated by the manic syndrome of a neurotic patient of pyknic type whose sister had a manic-depressive psychosis.

The organic reactions during electric convulsive therapy have interesting implications with respect to the question of the symptomatic psychoses during toxic-infectious diseases and confirm the view [5] that the symptoms of an exogenous psychosis do not depend on the noxious agent which caused it. Electric convulsive therapy shows that the same agent can produce clinical pictures of the greatest variety. It is not the damaging agent but constitutional and other factors within the patient which determine the picture. Only certain symptoms are constant in all organic reactions and are uninfluenced by personality factors.[6]

The prognosis of the organic syndromes during electric convulsive therapy is as favorable as the prognosis of other symptomatic psychoses. The intensity of the reaction has no bearing on the duration. Disappearance of symptoms is sudden. Complaints of memory impairment over a longer period are not more frequent in patients with severe organic reactions than in patients with mild ones.

The question arises whether the organic mental symptoms as such, or pathophysiologic changes supposedly producing them, are necessary for results in electric convulsive therapy. Reports on remissions in psychotic patients during and after head injuries [7] and experiences with psychosurgery suggest that organic interference with cerebral function is likely to improve a psychosis and may also be the effective agent in shock therapy. It seems, however, that clinical manifestations of an organic reaction type are not necessary for therapeutic results. In 50 schizophrenic patients, each treated with twenty convulsions and studied with this question in mind, no relation between the degree of severity of the organic mental symptoms and the therapeutic

3. Löwenbach, H., and Stainbrook, E. J.: Observations on Mental Patients After Electric Shock, Am. J. Psychiat. **98**:828, 1942.

4. Birnbaum, K.: Der Aufbau der Psychose, Berlin, Julius Springer, 1923.

5. Bonhoeffer, K.: Die symptomatischen Psychosen im Gefolge von akuten Infektionen und inneren Erkrankungen, Leipzig, F. Deuticke, 1910.

6. Hoch, P. H.: Personality Factors in Alcoholic Psychoses, Psychiatric Quart. **14**:338, 1940.

7. Guttmann, E.: Suicidal Head Injuries, J. Ment. Sc. **89**:85, 1943.

results was seen: Daily treatments which invariably led to severe confusional states did not increase the therapeutic effect. Good results with schizophrenic patients reported [8] to have followed such "confusional treatment" are also obtainable with the same number of treatments given at greater intervals.[1] Further evidence against the influence of organic symptoms is furnished by the two facts that patients under electric convulsive therapy generally improve after four treatments, i. e., before they show even a memory defect, and that nonconvulsive responses produce confusion but no therapeutic results.

Organic psychotic reactions are seen not only with electric convulsive therapy but with insulin treatment. The Korsakoff picture is frequent after "protracted coma." Slight hypomanic states, as well as Sakel's [8c] "activation of the psychosis" during insulin treatment, were shown to be organic reactions.[9] This is important for the study of the common factor in the various shock methods which might be concerned in the cerebral damage, though not necessarily in the degree of its clinical expression.

It is undeniable that the frequency of organic syndromes is an unpleasant side effect of electric convulsive therapy. Rarer application of treatment (twice a week) diminishes but does not prevent them and prolongs the treatment unduly. Occipital application of the electrodes [10] or administration of oxygen during the treatment [11] did not prevent confusion in a series of patients whom my colleagues and I treated in this way. It actually had been anticipated that the organic symptoms were not produced by the area of application of the current and its intensity but were the result of the repeated convulsive state.

Therapeutic use can be made of the organic reaction itself. The recommendation of occasional electric convulsion treatments as an adjunct to psychotherapy of neurotic patients [12] is based on the organic symptoms of relaxation, disinhibition and euphoria, which loosen the patient's tension and thus make him more accessible to psychotherapy. Improvement in neurotic patients, which neither in type nor in degree is comparable to the results obtained with the psychoses, can often be achieved simply by producing an organic reaction.[13] Another use of the organic "blurring" was made when withdrawal symptoms were prevented in 2 patients with morphine addiction by producing an organic reaction with three treatments on two successive days prior to sudden withdrawal of the drug.

A thorough knowledge of the organic psychotic syndromes during electric convulsive therapy is of the greatest practical importance, for their misinterpretation may lead to inappropriate application of the treatment. Patients who improve rapidly from a depression but who after more treatments show uncertainty and bewilderment of an organic type are often considered as still depressed and are unnecessarily subjected to further treatment. Psychotic symptoms during electric convulsive therapy which follow a period of improvement are usually organic in type; actual relapses do not occur during the treatment but only after its discontinuation. In cases in which a deep but quiet organic reaction clears up by passing through a phase of excitement, unnecessary initiation of a second course of electric convulsive or insulin treatment is often a consequence of the failure to recognize the organic nature of the acute episode. Another mistake is discontinuation of treatment because of an organic reaction which is taken for aggravation of the patient's condition. In cases of schizophrenia in which twenty, or even more, treatments are needed, such discontinuation is often responsible for inadequate treatment. It should be realized that in favorable and unfavorable cases alike, the outcome of electric convulsive therapy can be determined only two weeks after the last convulsion, i. e., when the organic reaction has definitely cleared up.

SUMMARY

A great variety of organic psychotic episodes can be observed during a course of electric convulsive therapy. The appearance of new symptoms during such treatment is usually indicative of an organic reaction. The correct interpretation of these syndromes is of paramount importance for proper planning of electric convulsive

8. (*a*) Löwenbach, H.: Electric Shock Treatment of Mental Disorders, North Carolina M. J. **4**:123, 1943. (*b*) Neymann, C. A.; Urse, V. G.; Madden, J. J., and Countryman, M. A.: Electric Shock Therapy in the Treatment of Schizophrenia, Manic Depressive Psychoses and Chronic Alcoholism, J. Nerv. & Ment. Dis. **98**:618, 1943. (*c*) Sakel, M.: The Pharmacological Shock Treatment of Schizophrenia, translated by J. Wortis, Washington, D. C., Nervous and Mental Disease Publishing Company, 1938.

9. Erb, A.: Zur Psychopathologie der hypoglykämischen Zustände bei Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:65, 1938.

10. Sogliani, G.: Elettroshockterapia e cardiazolterapia, Rassegna di studi psichiat. **28**:652, 1939.

11. Holovachka, A.: Oxygen in Electro-Shock Therapy, J. Nerv. & Ment. Dis. **98**:485, 1943.

12. Selinsky, H.: The Selective Use of Electroshock Therapy as an Adjuvant to Psychotherapy, Bull. New York Acad. Med. **19**:245, 1943.

13. Kalinowsky, L. B.; Barrera, S. E., and Horwitz, W. A.; Electric Convulsive Therapy of the Psychoneuroses, Arch. Neurol. & Psychiat. **52**:498 (Dec.) 1944.

therapy. Treatment is often unnecessarily continued because of symptoms which are no longer an expression of the original disease, or it is prematurely interrupted because transient organic episodes are taken as an aggravation of the patient's illness. They constitute one of the reasons why not the purely mechanical application of electric convulsive therapy but only thorough acquaintance with the psychiatric manifestations during the treatment can lead to its successful employment.

These organic reactions offer almost experimental conditions for the study of the various factors which determine the type of symptoms in a "symptomatic" psychosis. They have interesting implications for a number of neuropsychiatric problems.

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ORIGIN OF THE SPIKE AND WAVE PATTERN OF PETIT MAL EPILEPSY

AN ELECTROENCEPHALOGRAPHIC STUDY

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It is interesting that despite the current emphasis which has been placed on the electroencephalographic detection of cortical lesions and the successful identification of the epileptogenic focus for a certain group of patients displaying generalized convulsions, no such demonstrable cortical lesions have been shown to constitute the focus for attacks of petit mal epilepsy. The hypothesis that the focus for petit mal epilepsy may be subcortical, and therefore not capable of being identified by the usual electroencephalographic technics, receives support from evidence cited by Penfield and Erickson [1] (page 138). These authors reported a case of petit mal epilepsy for which the focus was identified by implanting electrodes in the region of the interpeduncular space. Records from the electrodes were obtained which demonstrated a local discharge at this point, and certain characteristics of the seizure were reproduced by stimulating this area.

The data to be presented in this paper constitute further evidence of the subcortical origin of petit mal seizures. This evidence is derived from electroencephalograms and is concerned with (*a*) the distribution of the spike and wave pattern of petit mal epilepsy after almost complete section of the corpus callosum and (*b*) the time of onset of the spike and wave pattern as recorded from a series of widely separated scalp leads.

METHOD

The technic of recording was similar to that in general use in electroencephalographic laboratories. The electrodes were small German silver cups attached to the scalp convex side up. They were secured in place with colloidin and filled with electrode jelly through a small central hole. Flexible wires led from the scalp buttons to a set of selector switches so arranged that each pair of leads could be connected to any of six independent amplifiers. The recorders consisted of moving iron piece speaker elements adapted for use as ink writers. The natural period of the pens was about 40 cycles per second, and their overshoot was reduced to a minimum by electromagnetic damping. Either monopolar or bipolar leads were employed, the choice depending on circumstances. During the test the patient reclined on a cot in a semidarkened, electrically shielded room. The amplifier and the recording apparatus used in this investigation were designed by Dr. A. C. Young.

RESULTS

The records from which the data were assembled all showed repetitive complexes clearly containing the spike and wave pattern, which has been found pathognomonic of petit mal epilepsy (Gibbs, Lennox and Gibbs [2]). The position and size of the spike with reference to the wave were variable. The frequency of the waves varied from 2 to 4 per second. No attempt was made to differentiate petit mal seizures, larval petit mal attacks and petit mal variants, either on a clinical or on an electrical basis.

In presentation of the results, the term "sequence" is used to refer to the complete set of petit mal waves associated with a single outburst. The term "signal" is frequently used when it is desired to refer to a single spike and wave.

Effect of Section of the Corpus Callosum on Distribution of the Spike and Wave Pattern.—If the spike and wave pattern of petit mal epilepsy were initiated at a discrete cortical site and the abnormal discharge then spread to other cortical regions, involvement of the contralateral hemisphere would be expected to occur via the fibers of the corpus callosum. This expectation was borne out for the spread of the train of abnormal waves set up by the brief local stimulation of the monkey cortex in the experiments of Erickson.[3] He found that section of the corpus callosum resulted in confinement of the abnormal waves to the hemisphere which contained the site of the original electrical stimulation. Similarly, in the

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1. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

2. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Localizable Features of the Electrical Activity of the Brain in Petit Mal Epilepsy, Am. J. Physiol. **116**:61 (March) 1936.

3. Erickson, T. C.: Spread of the Epileptic Discharge: An Experimental Study of After-Discharge Induced by Electrical Stimulation of Cerebral Cortex, Arch. Neurol. & Psychiat. **43**:429 (March) 1940.

case of the single action potential spike initated by local cortical stimulation (Curtis [4]) it was found that section of the corpus callosum resulted in confinement of the observed electrical response to the ipsilateral hemisphere.

It should therefore be possible to answer the question whether the petit mal attack was incident in the cortex by a study of the cortical distribution of the spike and wave pattern in the postoperative electroencephalograms of the patient after section of the corpus callosum. If the spike and wave pattern was obtained from both hemispheres after section, its appearance might be regarded as presumptive evidence that the complex in question had not originated in the cortex but had spread up into both hemispheres from a subcortical focus. Van Wagenen has performed section of the corpus callosum in a number of epileptic patients.[5] Fortunately, I was able to secure postoperative records on 2 of these patients during petit mal seizures. Representative spike and wave sequences taken from these records appear in figures 1 and 2.

The patient whose electroencephalogram appears in figure 1, a man aged 21, had been subject to epileptic attacks since the age of 5 years. At the time he was seen at the electroencephalographic laboratory he was having numerous petit mal seizures and only occasional grand mal attacks. The petit mal seizures were of from three to thirty seconds' duration and involved lack of orientation, with no other clinical signs [5b] (page 975). The portion of record presented in figure 1 *C* was chosen from numerous spike and wave sequences appearing in his postoperative records, taken on five different occasions. This portion was selected because it presents tracings from monopolar leads from six widely separated loci, and its value suffers from the fact that the spike and wave pattern is not well pronounced in the lead from the right precentral area. However, scrutiny of the original record, simultaneous time coordinates being taken into account, clearly establishes the presence of the petit mal pattern in this lead.

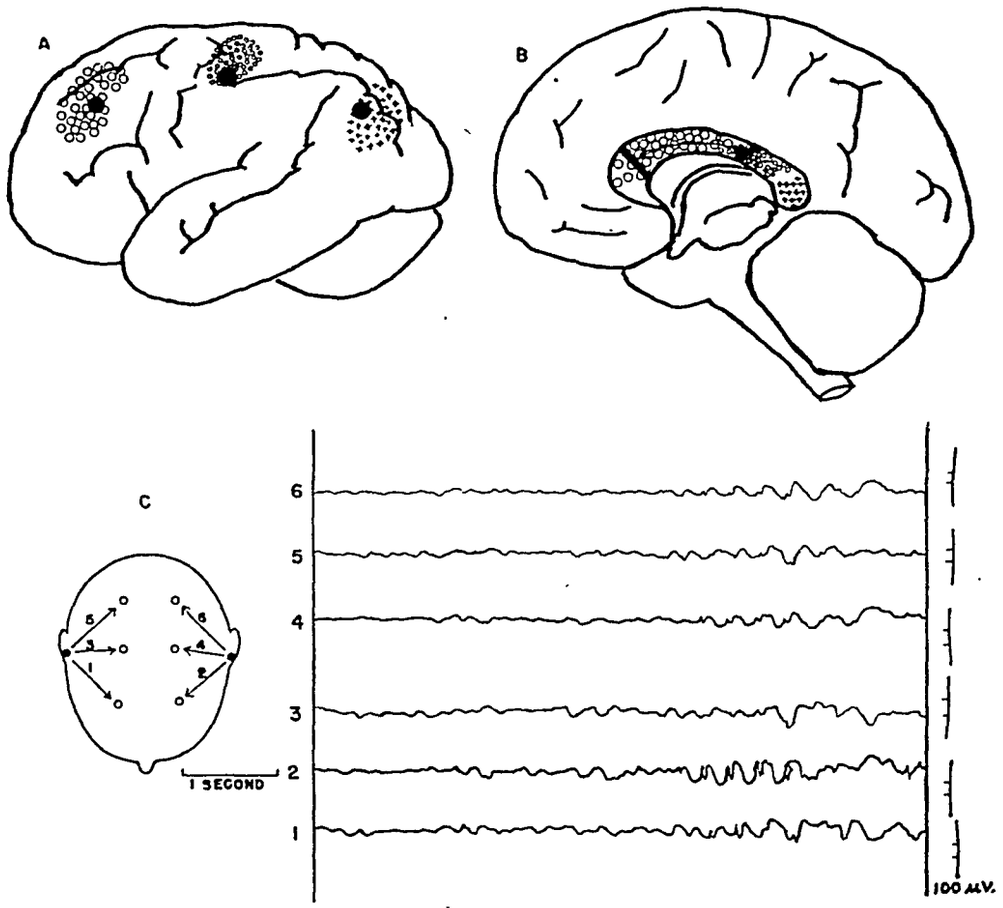

Fig. 1.—The record of a petit mal wave sequence taken from patient E. L., with partial section of the corpus callosum, as indicated by marks at the ends of the arrow. The positions of callosal fibers, as shown in *B*, are related to the cortical areas indicated by the same code in *A*. The large black dots in *A* represent the cortical projection of the electroencephalographic scalp leads. *C*, postoperative records, showing spike and wave sequences.

4. Curtis, H. J.: Intercortical Connections of the Corpus Callosum as Indicated by Evoked Potentials, J. Neurophysiol. **3**:407 (Sept.) 1940.

5. (*a*) For a preliminary report of this work, see Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum, Arch. Neurol. & Psychiat. **44**:740 (Oct.) 1940. (*b*) The cases of these 2 patients are described in detail in a second article (Akelaitis, A. J.; Risteen, W. A.; Herren, R. Y., and Van Wagenen, W. P.: Studies on the Corpus Callosum: III. A Contribution to the Study of Dyspraxia and Apraxia Following Partial and Complete Sections of the Corpus Callosum, ibid. **47**:971 [June] 1942).

In general, it may be said that bilaterally symmetric leads show in-phase spike and wave complexes of similar shape. Since the section in this case was not complete, it is important to identify the extent of the destruction of interhemispheral connections via the corpus callosum in terms of the areas from which the electroencephalographic tracings were recorded. *A* and *B* of figure 1 attempt to clarify this question. It has been assumed that the monkey cortex and the human cortex are comparable with regard to the arrangement of fibers in the corpus callosum according to the cortical area from which they are derived. The diagrams in *A* and *B* (fig. 1) were made on the basis of the experiments of Sunderland,[6] in which local cortical lesions were produced in monkeys and the extent of degeneration of fibers in the corpus callosum was investigated histologically. The position of the lesions as related to the scalp leads employed in the electroencephalographic study are represented in a drawing of the human cortex in figure 1 *A*. The large black dots refer to the approximate position of the electroencephalographic leads as projected on the underlying cortex. A code similar to that used to indicate the separate lesions is employed in figure 1 *B*, showing their representation as fibers in the corpus callosum. Figure 1 *B* also indicates the extent of the section of the corpus callosum as stated in the surgeon's operative notes. The entire area between the heavy lines at the ends of the arrow was included in the section.

It is apparent that little or no interference with conduction with respect to the precentral and parietotemporal areas would be expected. The callosal connections for the frontal area were seriously interfered with; therefore it might be reasonable to expect the disappearance or pronounced attenuation of the response in one frontal area if it is assumed that the spike and wave signal has a local cortical origin and spreads from one frontal area to the other via callosal fibers. Since the spike and wave complex appears in both frontal leads, as shown in figure 1, it may be concluded that the initial focus in this case was subcortical.

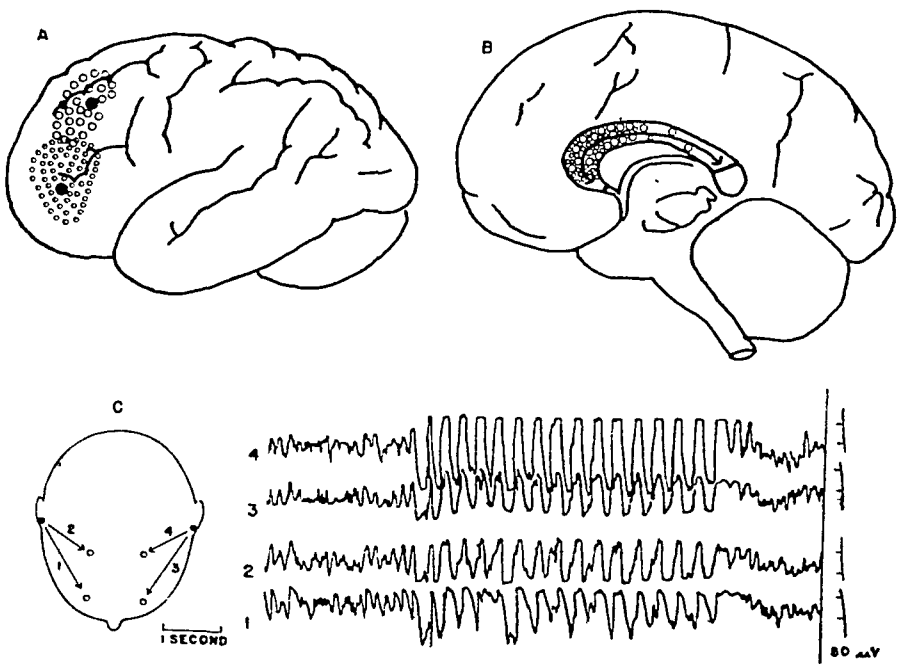

Fig. 2.—The record of a petit mal sequence taken from patient A. M., with partial section of the corpus callosum, as shown by marks at the ends of the arrow. The positions of the commissural fibers in the corpus callosum (*B*), in terms of the cortical areas from which they are derived (*A*), are identified by use of a code; large black dots in *A* represent the cortical projection of the electroencephalographic scalp leads. *C*, postoperative records.

Figure 2 presents comparable data in the second case. The seizures of this patient, a man aged 26, began at the age of 15 years. In addition to petit mal attacks, he was also subject to grand mal seizures, which developed with no preliminary warning or aura [5a] (page 751). It will be evident from figure 2 *B* that the callosal section was considerable in this case, extending from the anterior commissure to within 1 cm. from the tip of the splenium. The fornix was also divided just anterior to the foramen of Monro. It is probable, therefore, that the fibers of the corpus callosum for the prefrontal and frontal areas were sectioned in their entirety (granted a fundamental analogy between the human and the monkey cortex). Since the spike

6. Sunderland, S.: Distribution of Commissural Fibers in the Corpus Callosum in the Macaque Monkey, J. Neurol. & Psychiat. **3**:9 (Jan.) 1940.

and wave complex appears simultaneously in all four leads, the possibility of an initial focus in the frontal or the prefrontal area of the cortex is excluded.

There remains the question whether the focus might reside in some other cortical area and spread via rapidly conducting axons to the sites from which the leads were taken. The existence of rapidly conducting intrahemispheric and interhemispheric axons has been established by recent physiologic evidence. Curtis,[4] by electrical means, and McCulloch and Garol,[7] by local application of strychnine found that the stimulation of areas 5 and 6 and a small part of area 9 set up potentials which could be recorded from many areas on the opposite hemisphere. The short latencies between the stimulus and the response at mutually distant points indicate transmission via axons of the corpus callosum as the mode of conduction. Dusser de Barenne and McCulloch [8] presented evidence that axonal connections exist between areas in the same hemisphere subserving sensation in a particular part of the body.

These observations necessitate the consideration of two other possible modes of initiation and spread of the petit mal complex. The first possibility is that a cortical focus exists in those specific areas (that is, areas 5 and 6 and a part of area 9) which have connections via the corpus callosum to multiple areas on the opposite hemisphere. According to this view, the simultaneous appearance of the signal in the frontal and prefrontal leads depends on the conduction of the wave complex from its origin, say area 5 of the right hemisphere, to the corresponding area of the left hemisphere via the corpus callosum and the subsequent rapid bilateral conduction to the frontal and prefrontal areas by way of the multiple callosal pathways. This possibility may be excluded by examination of Sunderland's map of the distribution in the corpus callosum of the fibers from areas 5, 6 and 9. It becomes apparent that the section of the corpus callosum has destroyed all connections of the corpus callosum from these regions.

The second possibility is that of a focus in the occipitoparietal area, conduction to the corresponding area of the other hemisphere through callosal fibers of the intact splenium and, finally, intrahemispheric conduction to the frontal and prefrontal areas. In order to examine this possibility, a record was obtained from the patient with leads connected as shown in figure 3. An attempt was made to induce a petit mal attack by hyperventilation. Although no attack was induced, single petit mal complexes appeared in the record. Examination of figure 3 shows that single complexes appear simultaneously in the two prefrontal-frontal leads and that no petit mal complex can be detected in the occipital-parietal leads. The possible explanation based on the assumption of an occipitoparietal focus can therefore be regarded as untenable. A somewhat similar mode of spread might be suggested based on the supposition that the initial focus was in the temporal area and that the petit mal signal was conducted through the anterior commissure to the opposite hemisphere and then spread forward by means of intrahemispheric axon paths. This proposal may be disposed of, since figure 3 shows that the petit mal signal may appear simultaneously in the right and the left prefrontal-frontal leads but only in the left precentral-temporal lead.

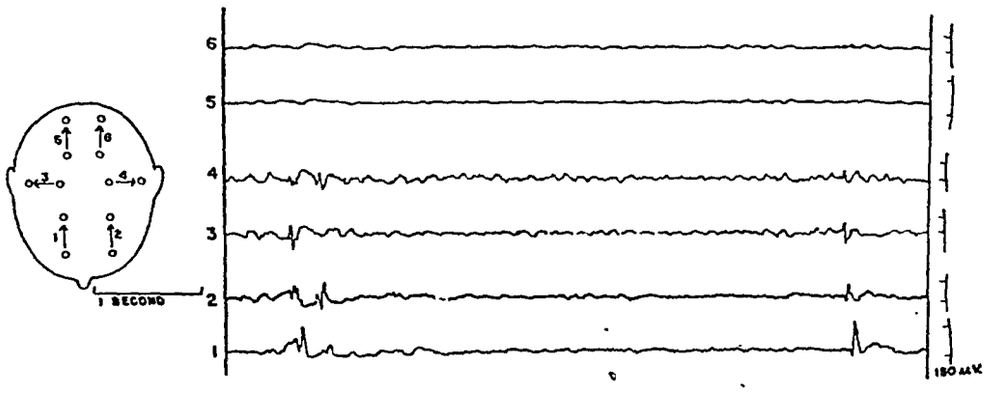

Fig. 3.—The record of petit mal waves for patient A. M., with leads placed as shown in the diagram.

Since other possible modes of spread of the spike and wave signal from the cortical focus have been shown to be incompatible with the electroencephalographic data available for this patient, it is concluded that the initial focus in this particular subject is subcortical. The proposal that in general petit mal epilepsy originates at a subcortical level receives support from a consideration of the time of onset of the spike and wave sequence as measured in the electro-

7. McCulloch, W. S., and Garol, H. W.: Cortical Origin and Distribution of Corpus Callosum and Anterior Commissure in the Monkey, J. Neurophysiol. **4**: 555 (Nov.) 1941.

8. Dusser de Barenne, G. S., and McCulloch, W. S.: Functional Organization in the Sensory Cortex of the Monkey, J. Neurophysiol. **1**:69 (Jan.) 1938.

encephalograms of a group of patients examined at the laboratory.

Simultaneous Onset of the Spike and Wave Pattern in Multiple Leads.—Study of the time of onset of the spike and wave signal at cortical sites at a distance from each other was carried out by analysis of 275 distinct sequences in the records obtained from 21 patients with petit mal epilepsy. The records of 13 patients showed a simultaneous onset of the signal in all leads employed and for all sequences recorded. The records of 6 patients showed a simultaneous onset in some of the sequences and delayed appearance in one or more leads in other sequences. For 5 of the 6 patients it was found that with any given leading arrangement in which appearance of the signal was delayed in one or more leads in a particular sequence, another sequence could be discovered which showed simultaneous appearance of the signal in all leads. Of the entire group of 21 patients, the records of 2 showed delayed appearance of the signal in one or more leads for all the sequences recorded. Since there were available for study only 1 sequence for 1 of these patients and 3 sequences for the other, it might be supposed that if a greater number of attacks had been recorded simultaneity of onset might also have been demonstrated for these patients. It may therefore be said that for 18 of 21 patients sequences could be selected showing a simultaneous appearance of the spike and wave signal for all leading arrangements investigated.

Figure 4 shows records of the petit mal sequences for 3 patients and demonstrates the simultaneous appearance of the signal in multiple lead sets. In figure 4 *A* the appearance of the petit mal sequence is shown to occur about one second after the beginning of the record. If the simultaneous ordinates shown at the right of the figure are considered, it can be seen that the initial spike is simultaneous in all four bipolar leads. Leads 1 and 2 show an in-phase slow wave; leads 3 and 4, an out-of-phase slow wave. This finding taken alone is compatible with the assumption of either (*a*) a single source located centrally with respect to the uppermost buttons of each pair of leads or (*b*) a greater amplitude of signal at the uppermost buttons, although

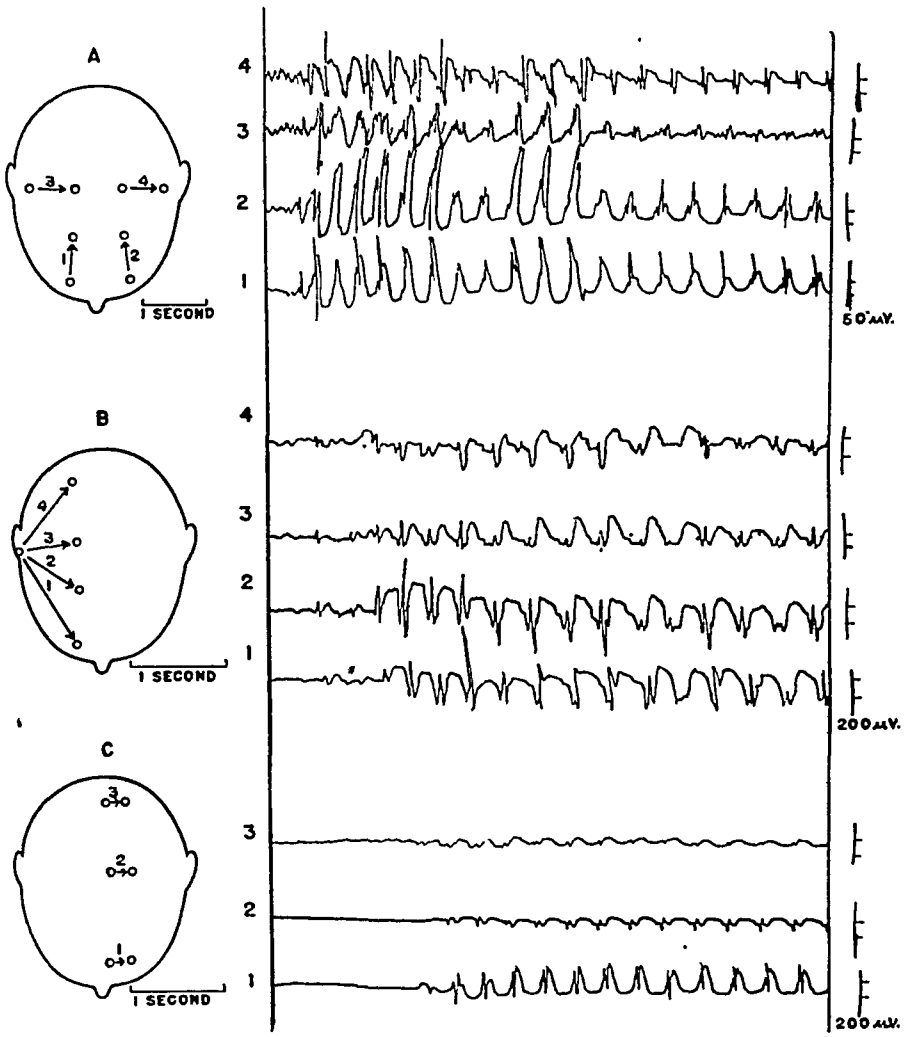

Fig. 4.—Record showing the simultaneous onset of the spike and wave complex in multiple leads of the electroencephalogram, arranged as shown in the diagrams. Simultaneous coordinates are shown at the right margin. Calibrations of amplitude are designated by the horizontal lines on the pen coordinates.

the petit mal complex appeared simultaneously in all areas from which leads were taken. It is probable that the latter assumption is the correct one, since another record obtained from this patient, using monopolar leads from the same areas of the scalp, showed the simultaneous appearance of the petit mal signal in all leads. Figure 4 *B* demonstrates simultaneity of onset with a monopolar system of leading. Records with bipolar leads, which were also taken on this patient, showed simultaneous appearance of the spike and wave signal in all leads.

Figure 4 *C* shows the beginning of a petit mal sequence as recorded from buttons placed only 3 cm. apart. When the differences in potential from points so close together are recorded and scalp leads are used, rather small excursions of the pen are to be expected. For this reason it is difficult to distinguish the first spike and wave in lead 2. Examination of the original record enables one to distinguish a small spike in lead 2 which occurs simultaneously with the first spike in leads 1 and 3. The tracings in *C* have been included since, with such a short distance between leads, the electrical condition would favor the recording of differences of potential originating from the cortex as distinct from differences in potential arising from deep cortical or subcortical regions.

The simultaneity of onset of the spike and wave pattern as recorded from relatively distant scalp leads has been noted in the literature (Gibbs and Gibbs,[9] Jasper,[10] pages 412 and 425). The observation is presented in this paper in order to examine its meaning in relation to the site or origin of petit mal epilepsy.

If the electroencephalogram permitted the measurement of the time of onset to within a millisecond and showed simultaneous initial spike and wave signals at a number of widely separated points, the possibility of a discrete cortical origin could be dismissed at once. Unfortunately, the first condition was not satisfied, for at least two reasons: (1) The fast paper speed of 4 cm. per second, even with the greatest care in the determination of simultaneous coordinates of the different pens, did not permit the estimation of time much closer than to ± 10 milliseconds; (2) the shape of the spike and wave complex as recorded from scalp leads is sufficiently rounded and distorted by local leading conditions as to make it difficult to select any point of the complex for which simultaneity to within 1 millisecond could be determined, even though cathode ray technic was used.

Since the figures in the text establish coincidence only to about ± 10 milliseconds, they may be regarded as evidence for the noncortical origin of the petit mal complex only if it can be shown that the rate of spread of the dysrhythmia from a cortical focus would be expected to be slow in terms of the minimum measurable time difference.

Repetitive cortical dysrhythmias produced in monkeys as an after-discharge, following local electrical stimulation of the cortex (Erickson [3]), show that the time occupied by the march of the paroxysmal waves from the artificial cortical focus to the farthermost point in the motor strip of the opposite hemisphere was of the order of seven seconds. Injection of thujone into the femoral vein of rabbits (Adrian and Matthews [11]) caused a paroxysmal type of cortical discharge, spreading at a rate of about 10 cm. per second.

The more rapid rates of spread for action potential spikes (Curtis and Bard,[12] Curtis [4]) which are conducted from one hemisphere to the other, with latencies of ten to forty milliseconds as measured from the shock artefact to the wave crest, do not apply to the case in hand, since (*a*) the petit mal complex is not a simple action potential spike and (*b*) in the experiments previously cited the spike was conducted via the corpus callosum. It has been shown that an intact corpus callosum is not a necessary condition for the simultaneous appearance of the spike and wave complex at comparable loci in the two hemispheres.

It may therefore be urged that the petit mal complex is much more analogous to the slowly spreading "after-discharge" waves than to the more rapidly conducted spikes and that the determination of simultaneity from the measurement of the electroencephalograms is sufficiently accurate to constitute evidence for the noncortical origin of the spike and wave complex.

COMMENT

In the presentation of the experimental data, two assumptions have been made without explicit acknowledgment, namely, that the petit mal complex derives from a single focus (without prejudice as to the cortical or the subcortical origin) and that the nerve elements in the cortical layer are active in the production of the electrical complex.

9. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941, p. 221.

10. Jasper, H. H.: Electroencephalography, in Penfield and Erickson,[1] chap. 14.

11. Adrian, E. D., and Matthews, B. H. C.: The Interpretation of Potential Waves in the Cortex, J. Physiol. **81**:440 (July) 1934.

12. Curtis, H. J., and Bard, P.: Intercortical Connections of the Corpus Callosum as Indicated by Evoked Potentials, Am. J. Physiol. **126**:473 (July) 1939.

Unless the first assumption is valid, any consideration of the location of the focus becomes meaningless. An alternative to the origin in a single focus is an alteration in the chemical environment of the cortical cells, mediated presumably by a change in the composition of the circulating blood and causing a general response of all the cells.

The simultaneity of the onset and of the disappearance of the signal at loci distant from each other makes the latter alternative unlikely. An even more powerful argument against this theory of the nonspecific genesis of the petit mal waves exists in the identity of pattern frequently observed in bilaterally symmetric leading arrangements. Figure 5 (*A* and *B*) shows examples of this identity in pattern. Rosenblueth and Cannon[13] sought to explain the widespread synchronization of the self-sustained cortical response by showing that all cortical regions have similar time constants and by postulating a shifting cortical pacemaker. According to this view, no single specific cortical pacemaker exists, and the area which fires first discharges over facilitated neuronal paths to all other areas. Without commenting on the validity of this interpretation, one should point out that important differences exist between the responses which the authors recorded after electrical stimulation of the cortex and the petit mal sequences under discussion. The synchronization that is cited by these experimenters exists only after the gradual cortical spread of the responses has taken place. The synchronization of the spike and wave complexes may exist from the very beginning of the cortical

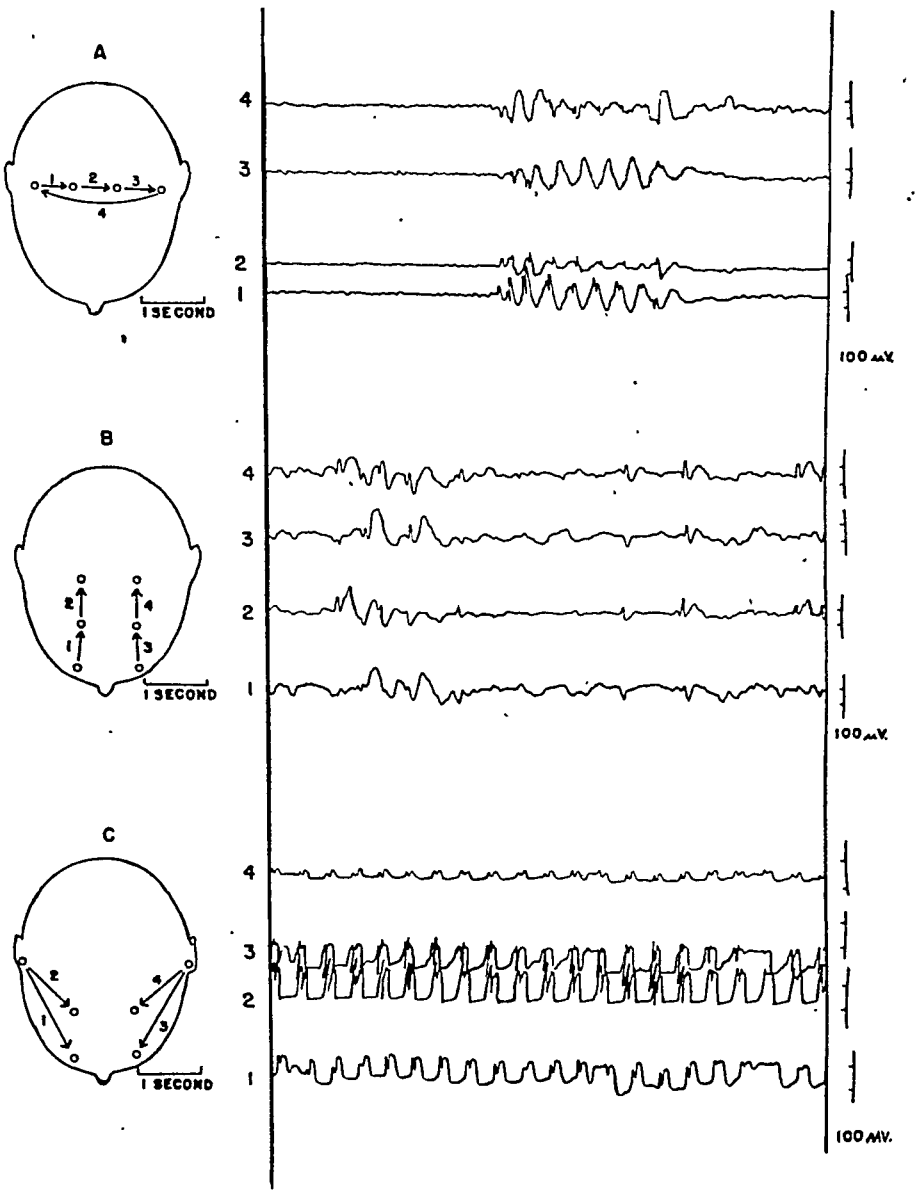

Fig. 5.—Records *A* and *B* illustrate bilateral symmetry of petit mal wave patterns. Record *C* shows a "dropped-out" petit mal wave in leads 1, 3 and 4.

13. Rosenblueth, A., and Cannon, W. B.: Cortical Responses to Electric Stimulation, Am. J. Physiol. **135:** 690 (Feb.) 1941.

response and therefore cannot be said to depend initially on facilitated intracortical conduction paths.

Figure 5 *C* shows a transient exception to the commonly observed bilateral symmetry of the electrical response. Here the lead from the right prefrontal area shows a "dropped-out" wave. This is duplicated in the left frontal lead but not in the right frontal lead. It is important to note that the wave following the omitted wave appears simultaneously in all four leads. The phenomenon illustrated in figure 5 *B* is suggestive of a transient conduction block such that no response occurs to one excitation wave proceeding from a pacemaker, although the next excitation wave passes through. Such a phenomenon would certainly not be expected if the local cortical areas were responding independently to a chemical change of the kind tentatively postulated.

The second assumption, i. e., that the cortical cells in the neighborhood of the leads produce the petit mal pattern, as distinct from a condition in which the excitation is restricted to a central oscillator and the electrical signal is led through the cortex, can be less satisfactorily established for all cases. There can be no doubt that in specific instances the local cortex is producing the signal. Such instances include cases in which the spike and wave complex does not appear simultaneously in all leads or in which the patterns in two bilaterally symmetric leads are transiently dissimilar, as appears in figure 5 *C*.

Any general theory of the genesis of the paroxysmal discharge associated with petit mal epilepsy must therefore take into account the apparent simultaneity of onset in distant cortical regions, the fact that the corpus callosum is not a necessary neural link in the conduction to all parts of the cortex and the necessity for the existence of some pacemaker in order to synchronize the discharge and to determine the small variations in pattern frequently found to be identical in symmetric leading arrangments.

If a subcortical pacemaker is postulated for all paroxysms of the petit mal type, certain limitations restrict the choice of a structure in which the focus may be tentatively placed. This structure must contain projection fibers with a widespread cortical distribution. The conduction paths from the pacemaker to the cortex must be approximately equal for all the cortical areas in question. The structure must display a degree of topical localization, since the recorded discharge may be confined to a discrete cortical locus. The postulated neuronal conduction paths cannot include motor neurons as an essential link, since no motor phenomena are encountered in the usual petit mal attack.

The thalamus presents itself as a possible site for such a pacemaker. It has frequently been postulated that the thalamus plays an important role in the maintenance of the spontaneous electrical activity of the cortex. Dusser de Barenne and McCulloch [8] showed that the spontaneous electrocorticogram of the monkey is changed or abolished after chronic cutting of the corticothalamic and thalamocortical fibers. Morison and Dempsey [14] showed that electrical stimulation of the thalamus in cats under light anesthesia induced with pentobarbital sodium may produce 8 to 12 per second cortical waves of widespread distribution, resembling the normal spontaneous cortical waves.

This observation is evidence that a close functional connection exists between the thalamus and the cortex. That topical representation exists in the thalamus is well known. It is, therefore, not unreasonable to assume the existence of the anatomic framework for the conduction of paroxysmal discharge from the thalamus to the cortex, with negligible small differences of latencies for mutually distant regions of the cortex. The hypothesis further requires that a discrete thalamic pacemaker discharge, that the excitation rapidly spread to the site of contralateral representation in the thalamus and that the paroxysmal involvement of such thalamic areas as are essential for "total" cortical representation occur before the characteristic spike and wave appears in any part of the cortex. In this connection, it may be said that Rosenblueth and Cannon [13] were unable to produce self-sustained discharges by electrical stimulation of the thalamus in monkeys under anesthesia induced with a compound of chloral hydrate and dextrose. Dempsey and Morison [15] found, however, that a single shock to the medial thalamus of a lightly anesthetized cat may produce a burst of 8 to 12 per second cortical potentials, lasting for two or three seconds. It is not clear in this case whether the after-discharge should be regarded as solely intracortical or intrathalamic as well. There is no question that the depth of anesthesia and the frequency and strength of the stimuli applied may be important experimental factors in the further elucidation of this point.

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SUMMARY

The postoperative records of 2 patients with nearly complete section of the corpus callosum show "petit mal" sequences displaying a simultaneous onset in bilaterally symmetric leads. Since conduction between the two hemispheres via axon paths in the corpus callosum has been destroyed, the existence of a cortical focus cannot be assumed in these particular patients. It is most likely that in the records of patients without section of the corpus callosum in which a similar simultaneous onset was displayed, conduction of the signal did not occur through the corpus callosum and that the source of this signal was subcortical in these patients, as well as in the patients subjected to operation.

The thalamus or the hypothalamus is considered as a tentative site for the pacemaker of the spike and wave complex.

Radiation Laboratory, Massachusettts Institute of Technology.

Dr. William P. Van Wagenen cooperated in the taking of records from the hospital patients used in this investigation.

ELECTROENCEPHALOGRAPHIC STUDY OF PREFRONTAL LOBOTOMY

A STUDY OF FOCAL BRAIN INJURY

LIEUTENANT ROBERT COHN (MC), U.S.N.R.

Because of the high incidence of head wounds (and resultant cerebral damage) sustained by casualties in the war, present interest in the study of injury to the brain has become great. Clinical studies, in which the electroencephalogram was used as an indication of disturbance in cerebral physiology following cranial lesions, have been extensively reported.[1] Much experimental laboratory work has been done to support and supplement these clinical data.[2] Despite the general excellence of these studies, many problems remain for solution because of the deficiencies inherent in the methods employed. The most apparent defect in the clinical work is that few of the subjects were known to the investigators prior to the post-traumatic study. In the experimental work animals were used as subjects; consequently, the results were not directly applicable to the phenomenon of cerebral injury as seen in man.

The electroencephalographic work presented in this report was carried out in conjunction with therapeutic prefrontal lobotomy.[3] The importance of this work to the general study of injuries to the brain becomes apparent when one considers the following conditions:

1. Controlled, well circumscribed and clearly defined lesions of the brain were produced.
2. Fifteen subjects were studied before and for a year or more after injury to the brain.
3. All studies were on human beings.

In this discussion on prefrontal lobotomy no attempt will be made to evaluate the clinical effectiveness of the method in the treatment of the psychoses.[3] The only concern is: What is the electroencephalographic evidence of cerebral damage, and in what way can such knowledge be utilized in the interpretation of electroencephalograms in cases of less precisely placed lesions (accidental trauma)?

METHOD

This report is based on the study of 30 human beings (civilians) with various psychiatric conditions, whose ages ranged from 20 to 65 years. Each subject underwent bilateral therapeutic prefrontal lobotomy.[4]

To date, a record has been taken from each subject every three to four months subsequent to the operation. Fifteen patients had electroencephalographic recordings only after the cerebral injury (operation). For the latter group the elapsed time from operation to recording ranged from one month to six years.

All tracings were made with a Grass three channel electroencephalograph.

RESULTS

The anatomic existence of a primary focal lesion was obvious from the nature of the operation.[3] However, that the electrical pathophysiologic response was also focal had to be demon-

From the Blackburn Laboratory, St. Elizabeths Hospital, Washington, D. C.

This work was aided in part by a grant from the Supreme Council, Thirty-Third Degree Scottish Rite, Masons of the Northern Jurisdiction, U. S. A.

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4. Prefrontal lobotomy in the patients under consideration was performed by Watts and Freeman (J. Internat. Coll. Surgeons **5**:233-240 [May-June] 1942), through burr holes in the coronal suture. The cortex was punctured in an avascular area close to the junction of Brodmann areas 9, 44, 45 and 46, and the subcortical white matter was severed rather completely in the plans of the coronal suture. This separated the frontal pole, comprising areas 9, 10 and 46 on the lateral surface and area 32 on the mesial surface, from the rest of the brain. The incisions seldom went down so far as to undercut areas 10, 11 and 12, at the base of the frontol lobe, or up so far as to affect area 8 to any notable degree. The surgeon attempted to avoid injury to the cortex both to prevent bleeding and to diminish likelihood of subsequent epileptic seizures.

In several of the cases reported here, secondary operations were performed through burr holes placed 3 cm. from the midline and 1 to 1.5 cm. behind the coronal suture, the subcortical incisions being made close to the junction between areas 6 and 8. Freeman and Watts (personal communication to the author) have observed a high incidence of epileptic seizures in patients undergoing secondary operations.—Walter Freeman.

strated. This was accomplished, as shown in figure 1. In this recording electrodes were radially arranged in four straight rows around one burr hole. The first electrode in each row was placed ½ inch (1.27 cm.) from the margin of the defect in the skull. Each succeeding electrode was separated 1 inch (2.5 cm.) from its abnormal electroencephalographic response to prefrontal lobotomy was focal (frontal), in conformity with the anatomic lesion.

In all subjects from whom records were taken within ten days after operation, high voltage slow wave discharges were observed in the symmetric frontal leads (fig. 2). The frequency

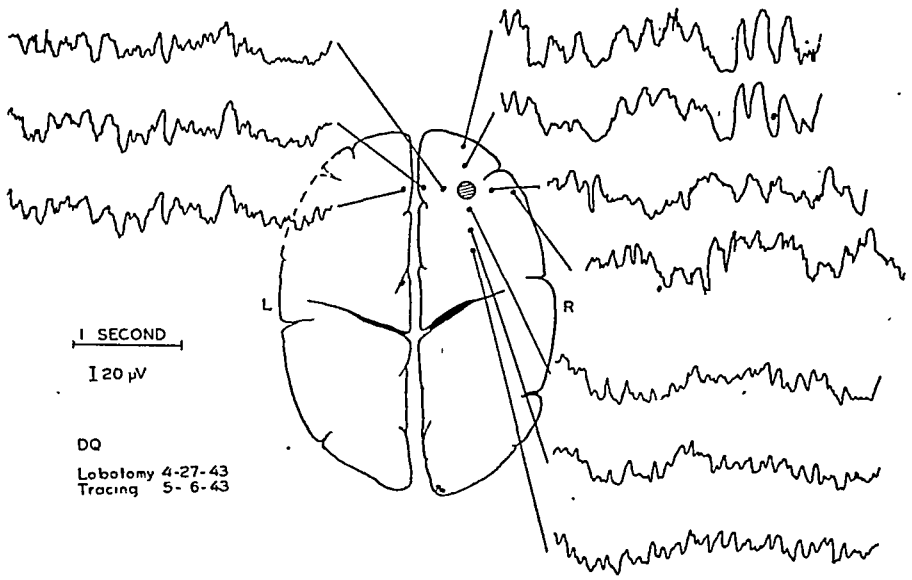

Fig. 1.—Focal electroencephalographic response to focal injury to the brain. The maximum abnormality is in the most rostral leads.

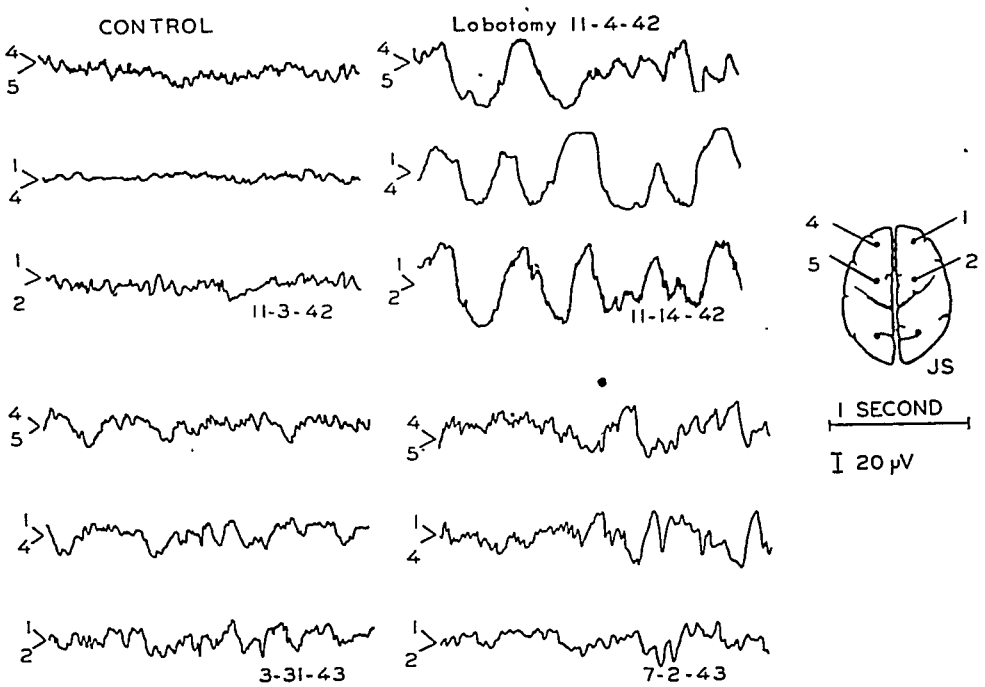

Fig. 2.—Typical electroencephalogram after prefrontal lobotomy. Moderate slow wave activity usually persists in the region of structural damage.

predecessor. All leads were taken with respect to the right ear. It was observed that the greatest number of high voltage slow waves were in the most rostral parasagittal leads; as one proceeded caudally and paracoronally, the prominence of the low frequency activity decreased. Hence it was established that the "immediate" ranged from 2 to 4 waves per second. In this same group, usually within one to three months after operation, the prominent low frequency oscillations were replaced with short sequences of 6 per second waves of reduced amplitude. In most subjects this low intensity abnormality persisted as a subdominant characteristic as long as

recordings were made. The variations in parietal and occipital potentials maintained their preoperative frequency, but usually developed greater prominence (higher voltage) after operation.

In 3 subjects from whom recordings were obtained with frontal leads within a month after operation no evidence of abnormal wave forms

Certain subjects (fig. 4) who within a relatively short time after operation showed only medium voltage slow waves, primarily in transverse leads, later exhibited prominent and persistent high voltage, approximately 4 per second waves in all frontal derivations.

For 1 subject (fig. 5) from whom no preoperative records were obtained, a postoperative

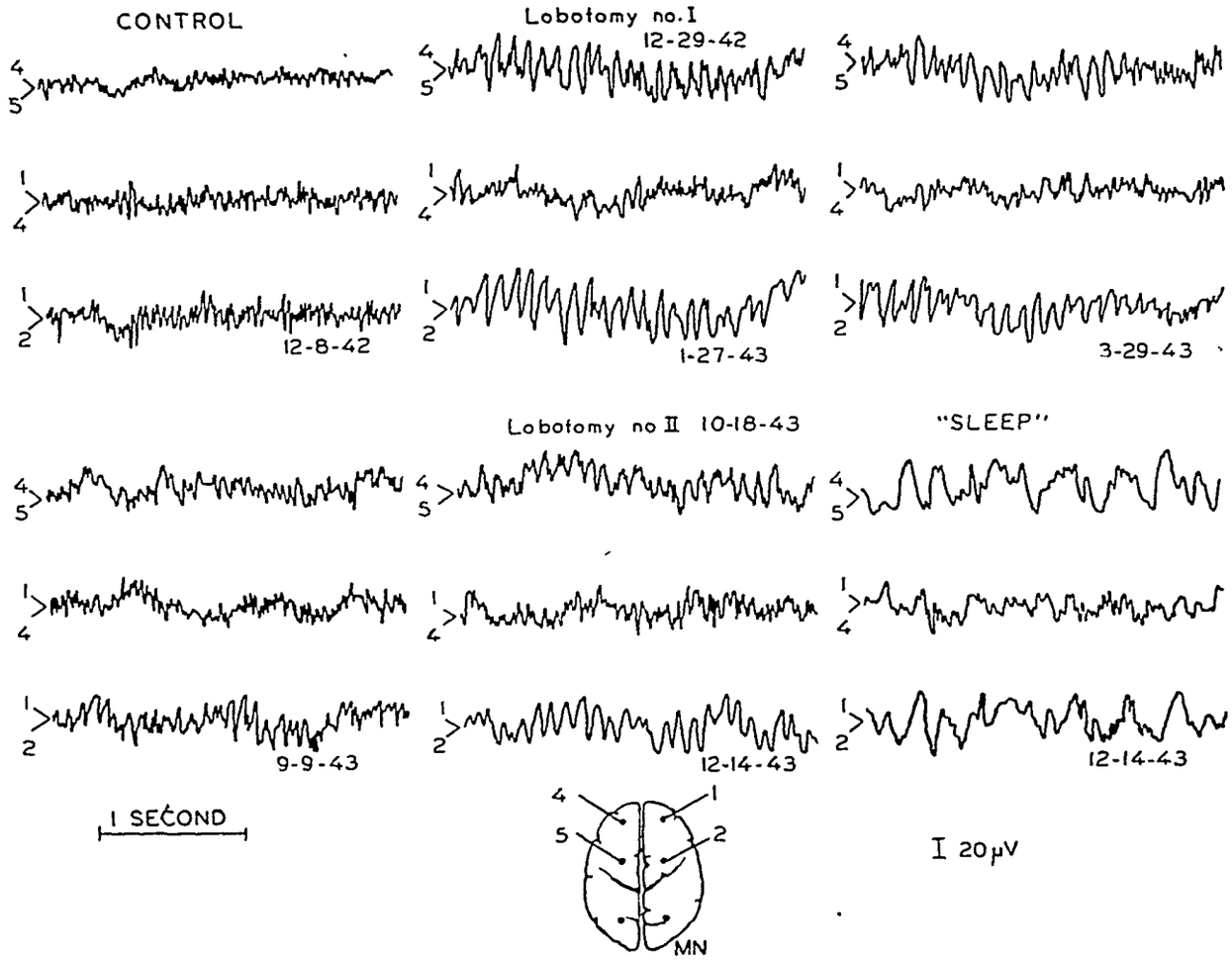

Fig. 3.—Enhancement of alpha activity following prefrontal lobotomy. Slow wave discharges during "sleep" are observed in the tracings in the lower right portion of the figure.

was recognized. Figure 3 shows portions of the electroencephalogram of 1 of these patients. It was seen that the preoperative high frequency pattern was replaced after the operation by entirely normal-appearing alpha waves. About nine months later, however, there was a regression to the high frequency pattern of the control type. A second lobotomy, ten months after the first, again failed to produce any abnormal electric response. This phenomenon of no demonstrable change in the electroencephalogram following injury to the brain raised the question whether slow wave activity could develop in such a brain. That no delta wave–inhibiting mechanism was active in this particular subject at least was beautifully shown in the low frequency discharges associated with moderately deep "spontaneous" sleep (group of waves in lower right portion of figure).

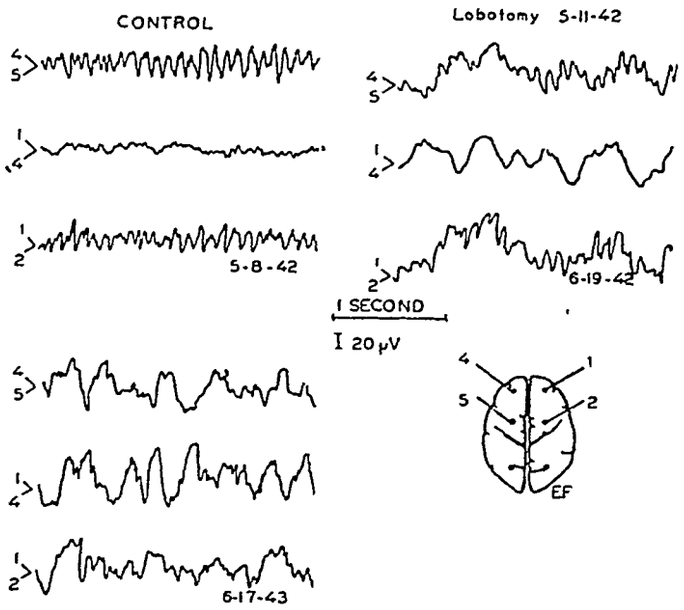

Fig. 4.—Moderately abnormal electroencephalogram five weeks after lobotomy (most prominent in the transverse frontal lead). Slow wave discharges dominated the output of potential approximately one year after operation.

tracing (one month after the second lobotomy) showed some slow discharges in the frontal leads, ranging in duration from one hundred and sixty to two hundred and fifty milliseconds. Nearly five months after the electroencephalographic recording he had a clinical epileptic seizure. An electroencephalogram taken six weeks after the convulsion showed a dominant delta wave pattern in the frontal regions.

Hyperventilation was used as a routine procedure only in the later preoperative and post-

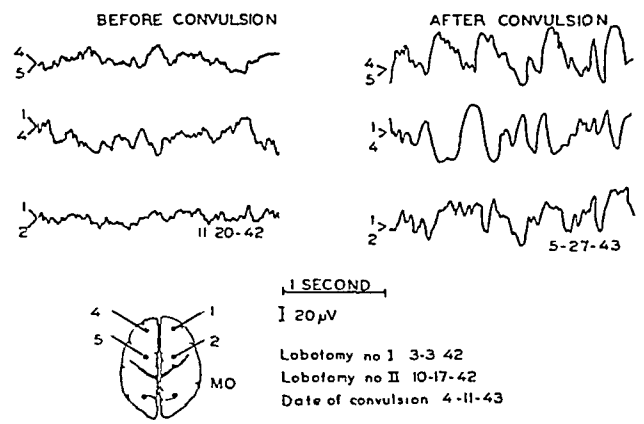

Fig. 5.—Before the onset of convulsive disorder abnormally slow waves were subdominant. After the seizure slow activity was prominent.

Of the 15 patients from whom no preoperative records were taken, it was observed that 10 showed pronounced electroencephalographic abnormalities even four to six years after injury to the brain (operation). Patient EC (fig. 7) clearly presented generalized abnormality in the electroencephalogram, with the maximum abnormality in the right frontal area. In the record for AH, in the same figure, approximately 1½ per second waves (i. e., 3 waves in two seconds), completely dominated the potential output of the frontal region. In the other 5 subjects, for whom the interval after operation ranged from two to six years, a potential of relatively high frequency characterized the tracing (fig. 7, *EA*). Predominantly the oscillations were random in frequency; however, trains of rhythmic, approximately 20 per second waves were occasionally observed.

COMMENT

It has been shown that the common "immediate" electroencephalographic response of the brain to a focal injury is maximum slow wave activity in that region. Within a variable interval, one to three months, most subjects show a definite diminution of abnormal discharges of

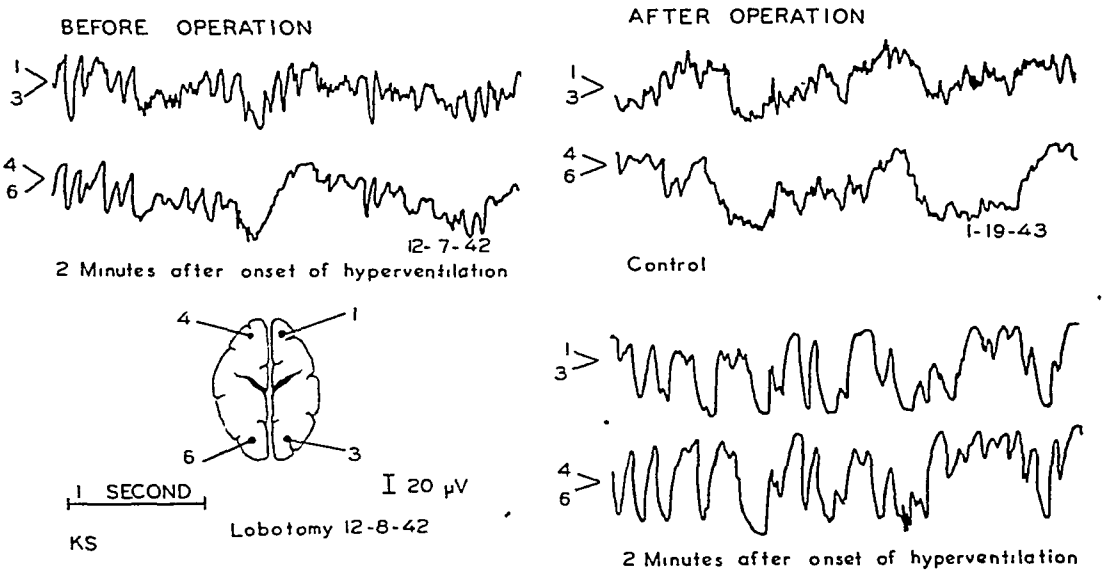

Fig. 6.—Effect of cerebral injury (operation) on response to hyperventilation.

operative recordings. Figure 6 shows samples from such a tracing. Before the lobotomy deep breathing for two minutes had no appreciable effect on the characteristic output of potential. After the surgical injury to the brain one observed in the "spontaneous" record, low voltage, nonsinusoidal, slow waves in the symmetric fronto-occipital leads. Moderate base line swinging was also seen in the control pattern. Two minutes after the onset of overventilation prominent sequences of delta waves dominated the record.

potential over the damaged area of the brain. Furthermore, for the lobotomized patient it has been shown that in the presence of minimal abnormal activity in the "spontaneous" record hyperventilation greatly accentuates the low frequency characteristic of the electroencephalogram. These results conform to and confirm, in all essentials, the electroencephalographic findings in the record of the majority of patients with acute head injuries.

Before the true import of prefrontal lobotomy as an experiment in controlled injury

to the brain was recognized, it was difficult to evaluate properly the marked focal or general abnormalities in the records of patients with a history of old head trauma. The question always arose as to whether the electroencephalographic abnormality was a direct result of the cerebral insult or an expression of a pretraumatic physiologic (epileptoid) disturbance. As is evident in the work presented, old cerebral lesions do give rise to focal and general electroencephalographic changes; consequently, the presence of prominent electroencephalographic abnormalities with old head injuries must be considered primarily as causally related to the cerebral damage unless pretraumatic tracings were made.

A further important fact pertaining to brain injury emerged from the studies on prefrontal lobotomy, namely, that even in the presence of known cerebral damage (acute and chronic) electroencephalographic abnormalities may be minimal or absent. As shown in figure 3, certain normal characteristics may actually be enhanced after injury to the brain.

The electroencephalographic phenomenon seen in the case of MO (fig. 5) was earlier observed by me in 2 cases of bullet wounds of the brain. In each instance pronounced slow activity did not appear until after the onset of a clinical convulsive disorder. If one allows the assumption that the slow waves came on concomitantly with or just previous to the seizure, then the hypothesis of Gibbs, Gibbs and Lennox [5] that cerebral dysrhythmia is the cause of the epilepsies appears to be confirmed. The absence of any seizures in other subjects with pronounced focal and general electroencephalographic abnormalities, such as AH and EC, whose records appear in figure 7, EF whose records appear in figure 4, and others not shown, strongly indicates, however, that the cerebral dysrhythmia is not the cause, but is one factor (or sign) in the development of convulsive states, and that an ill defined constellation of variables, not yet clearly recognized, must interact in order to give expression to the syndrome of the clinical epilepsies.

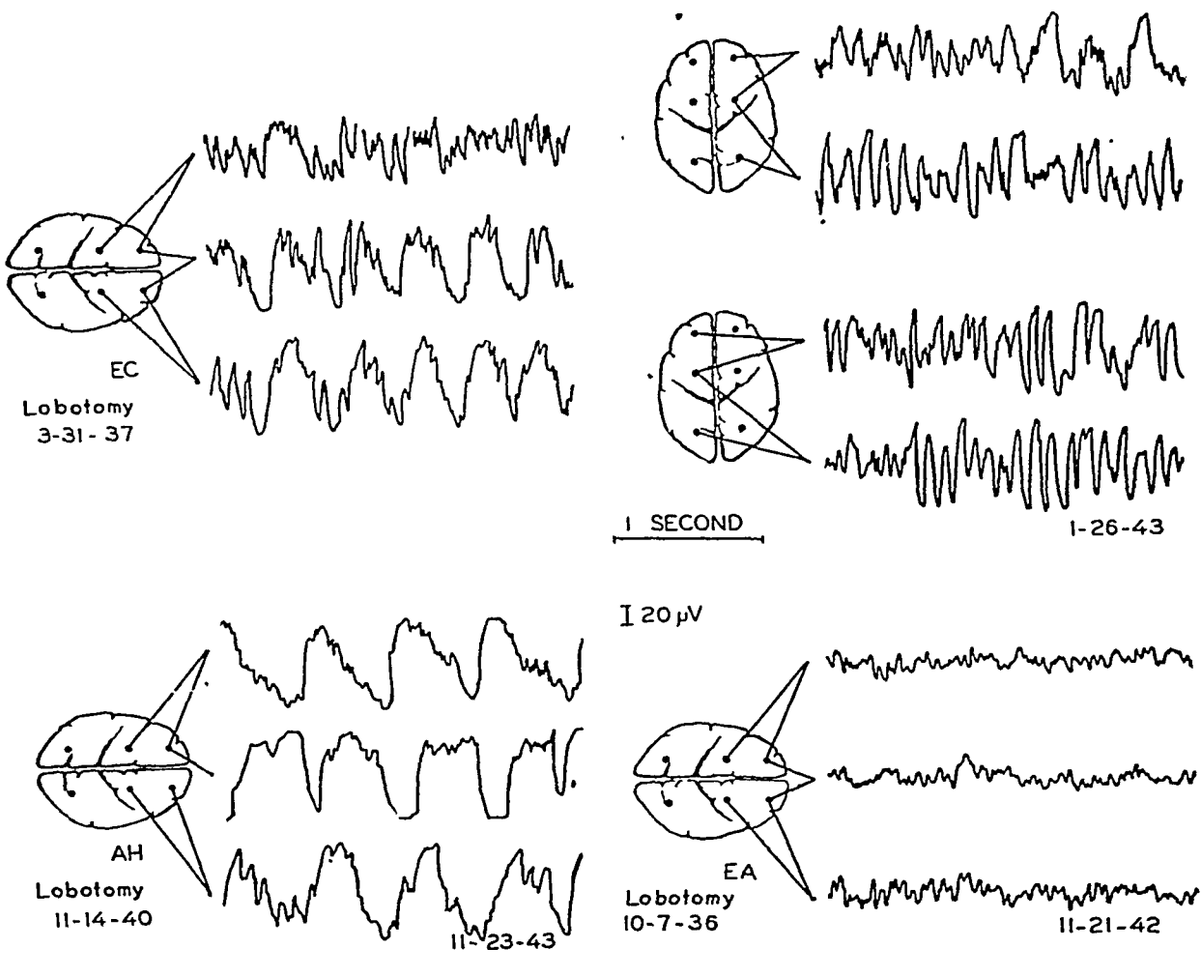

Fig. 7.—*EC*, electroencephalogram showing generalized abnormality nearly six years after operation; *AH*, prominent slow wave activity three years after operation (all possibility of artefact potentials has been carefully excluded); *EA*, random high frequency oscillations six years after cerebral damage.

In recent years the importance of hypoglycemia for the development of slow wave activity during hyperventilation has been heavily empha-

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sized.[6] The results shown in figure 6 forcefully bring out the fact that injury to the brain (neuronal disturbance) is an important factor in the production of slow waves during the process of deep breathing. This clear finding thus makes it necessary partially to deemphasize the role of blood sugar in the production of slow waves during overventilation and to weigh the relative importance of neuronal damage and elementary metabolic disturbances in each individual case under study.

The persistent low frequency activity observed as a late phenomenon of prefrontal lobotomy raised the question whether damage of subcortical gray masses influenced the production of these abnormal potential changes.[7] With thorium dioxide or iodized oil as the contrast medium in the path of the leukotome section, roentgenographic studies by Dr. Walter Freeman showed involvement of the caudate nucleus, unilateral and bilateral, in several subjects. However, no definite correlation between slow wave activity and injury to the striate body was observed. In the 1 case of this series in which autopsy was performed a gross lesion in the right caudate nucleus was observed. This patient's tracing was characterized by a random high frequency pattern and showed no focal or general slow wave discharges.

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CONCLUSIONS AND SUMMARY

1. The primary electroencephalographic response of the human brain to localized injury (prefrontal lobotomy) is the production of focal slow waves. These may or may not persist.

2. With lobotomized patients the return of the electroencephalographic pattern to a relatively normal pattern usually requires one to three months.

3. Certain persons show no demonstrable response to cerebral injury under the conditions of these experiments.

4. A representative group of subjects show apparent normal early recovery and then again exhibit grossly abnormal variations in potential in the region of the original injury. At times the abnormality may be general.

5. Hyperventilation after cerebral injury induces pronounced slow wave activity in brains that before injury were uninfluenced by a similar procedure.

6. Of the present group of 30 patients, 1 had clinically recognized convulsions.

7. The aforementioned phenomena are general and thus apply to injury to the brain from other traumatic agents.

Dr. Walter Freeman and Dr. James W. Watts cooperated in this study.

TRANSTENTORIAL HERNIATION OF THE BRAIN STEM

A CHARACTERISTIC CLINICOPATHOLOGIC SYNDROME; PATHOGENESIS OF HEMORRHAGES IN THE BRAIN STEM

I. MARK SCHEINKER, M.D.

CINCINNATI

While death due to medullary compression associated with herniation of the cerebellar tonsils has long been known, relatively little attention has been paid to the sequela of compression of the brain stem caused by herniation of the stem through the tentorial opening. In 1920 Meyer called attention to medial displacement and herniation of the hippocampal gyrus into the tentorial incisura in cases of space-consuming intracranial lesions. The subject was later elaborated by van Gehuchten,[1] Jefferson,[2] Reid and Cone,[3] Moore and Stern[4] and Smyth and Henderson.[5] All these contributors have amply demonstrated that space-consuming lesions may cause appreciable herniation of the hippocampal gyrus of the temporal lobe into the potential space that lies directly above and between the free edges of the tentorium cerebelli and the brain stem.

The same type of herniation has been recently observed by Schwarz and Rosner[6] in 100 cases of supratentorial space-consuming lesions. The clinicopathologic relations were studied in 43 selected cases. These authors frequently observed the following signs and symptoms: fluctuation in the state of consciousness; anisocoria, with or without dysfunction of the pupillary light reflexes; imbalance of extraocular muscles; cardiorespiratory and thermoregulatory disturbances; paradoxic and shifting signs of involvement of the pyramidal tracts; decerebrate rigidity, and stiffness of the neck. These signs and symptoms occurred irregularly and were exaggerated by lumbar puncture, encephalographic and ventriculographic procedures or craniotomy.

In a recent study[7] attention was called to the occurrence of the same type of herniation in cases of epidural and subdural hematoma. It was demonstrated that the shift of the temporal lobe and the associated hippocampal herniation were not the result solely of the space-consuming action of the hemorrhage but were contributed to by the edematous increase in bulk of the traumatized cerebral hemisphere.

It is the purpose of this study to demonstrate that the gravity of the clinical syndrome is not the result solely of the herniation of a relatively small portion of compressible tissue, such as the hippocampal gyrus of the temporal lobe; a much more important element is the frank herniation of the rostral portion of the brain stem through the tentorial opening, associated with edema and hemorrhages in the midbrain. This pathologic condition should therefore not be designated merely as "hippocampal herniation" or "temporal pressure cone" but, rather, should be called "transtentorial herniation of the brain stem." It will be shown that transtentorial herniation of the brain stem occurs with different types of cerebral lesions, irrespective of their cause, and that it is accompanied by the development of severe edema and hemorrhage in the brain stem. The character and severity of the lesions in the midbrain, as well as their distribution, are influenced primarily by the degree of compression of the larger veins of the brain stem and the extent of interference with venous outflow.

It is the hope that this pathologic study will furnish a broader basis for a clinical and physiologic approach to the problems involved.

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

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MATERIALS AND METHODS

This report is based on the study of 55 cases of transtentorial herniation of the brain stem, which may be classified under the following heads:

A. Cerebral vascular disease
   1. Massive cerebral hemorrhage
      (*a*) In association with arterial hypertension
      (*b*) In association with cerebral arteriosclerosis
   2. Cerebral softening due to vascular occlusion in association with cerebral arteriosclerosis

B. Trauma

C. Space-consuming lesions
   1. Brain tumor
   2. Brain abscess

PROTOCOLS

A. CEREBRAL VASCULAR DISEASE

MASSIVE CEREBRAL HEMORRHAGE DUE TO ARTERIAL HYPERTENSION

CASE 1.—A. T., a woman aged 48, was first admitted to the hospital on Jan. 8, 1943 with a history of severe pain in the left eye and gradual loss of vision. Examination gave normal results except for advanced hypertensive retinopathy. The blood pressure was 200 systolic and 120 diastolic.

The patient was readmitted to the hospital on April 14, 1943, in profound coma. The blood pressure was 225 systolic and 140 diastolic. The right pupil was dilated and reacted slowly to light. Advanced papilledema in the right eye was associated with numerous retinal hemorrhages.

Spinal puncture disclosed an initial pressure of 550 mm. of water. The fluid was grossly bloody. The patient died on the day of admission.

Necropsy revealed myocardial hypertrophy and cardiac dilatation associated with arteriolar nephrosclerosis.

Examination of the brain showed fulness of the right hemisphere, especially evident in the right temporal lobe. There was a well defined indentation in the herniated and swollen uncus on the right side, and the brain stem was shifted to the left.

Coronal sections through the cerebrum revealed massive intracerebral hemorrhage in the right cerebral hemisphere, with rupture into the ventricular system. Figure 1 demonstrates the hemorrhage and the pronounced swelling of the right hemisphere and the right half of the brain stem, associated with shift of the midline structures downward and to the left. There were scattered areas of small hemorrhages in the brain stem and the pons. The right half of the brain stem appeared softened and swollen (fig. 1).

Histologic examination disclosed vascular lesions typical of hypertensive encephalopathy and pronounced thickening and hyalinization of the arterioles and capillaries, with narrowing or obliteration of their lumens. Van Gieson preparations showed proliferation of the pericapillary connective tissue fibrils.

In the gray and white substance of both hemispheres were diffusely scattered foci of tissue disintegration, which consisted of small areas of rarefaction and softening associated with a slight degree of glia cell proliferation. In some areas there was to be seen a more extensive and severe form of destruction, associated with formation of small areas of cystic softening. The majority of these foci suggested a perivascular distribution.

Sections taken from the scattered small hemorrhagic areas of the brain stem and pons showed coalescent, small hemorrhages, most of which disclosed clearly their relation to tremendously congested veins (fig. 2). The vessel wall revealed all degrees of disintegration; in some of the perivenous hemorrhages only the shadow of the wall was to be seen in the center. In the vicinity of almost all the hemorrhages the tremendously engorged veins were surrounded by large masses of extravasated red blood cells, extending into the distended perivascular spaces.

The nerve parenchyma showed a high degree of rarefaction and edema, especially pronounced in the vicinity of the hemorrhages. There was no glial or mesodermal reaction to be seen in the areas of hemorrhage.

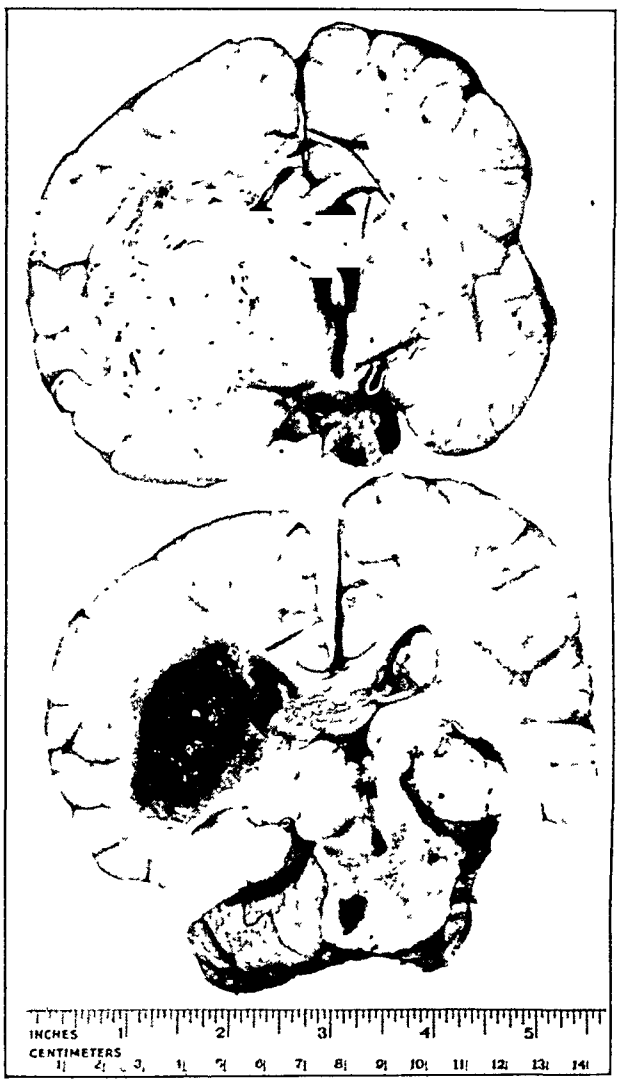

Fig. 1 (case 1).—Massive intracerebral hemorrhage with pronounced swelling of the right hemisphere. Note the swelling and softening of the right half of the brain stem, with shift of the midline structures downward and to the left, and scattered areas of small hemorrhages in the brain stem and pons.

MASSIVE CEREBRAL HEMORRHAGES ASSOCIATED WITH CEREBRAL ARTERIOSCLEROSIS

CASE 2.—M. S., a white woman aged 72, was admitted to the hospital in coma. She was apparently in good health until two weeks before admission, when she acquired a cold. On the day of entrance to the

hospital she was found lying on the floor, unconscious. Examination on admission showed equally dilated, fixed pupils, gasping respiration and an enlarged heart. The systolic blood pressure was 56 mm.; the diastolic pressure was not measurable. The patient died three hours after admission to the hospital.

Necropsy revealed arteriosclerosis, with coronary and aortic atherosclerosis, focal fibrosis of the myocardium and acute cardiac dilatation.

Examination of the brain revealed prominence and fulness of the right parietal lobe. The inferior surface showed a striking fulness of the right temporo-occipital region and shift of the optic chiasm and peduncles to the left. There was a broad uncal herniation on the right side, measuring 2 cm. in length and 1 cm. in width. Coronal sections through the hemispheres revealed an extensive hemorrhage, involving chiefly the right temporoparietal region and extending into the lateral portion of the basal ganglia. There was a striking shift and compression of the ventricular system (fig. 3). The brain stem was distorted, and the aqueduct was displaced sharply to the left. The right half of the brain stem was swollen, and its appearance suggested an early stage of softening. The central portion showed a grayish black discoloration, and numerous small hemorrhages were present.

Microscopic examination revealed far advanced arteriosclerosis. The right half of the midbrain presented swelling and tissue rarefaction. The corresponding half of the brain stem showed loss of myelin sheaths (fig. 4) and the presence of diffusely scattered, numerous petechial hemorrhages, localized chiefly about tremendously congested small veins; the most lateral portion of the left peduncle showed a small area of necrosis (fig. 4), probably due to mechanical compression (Kernohan's notch).

CEREBRAL SOFTENING DUE TO VASCULAR OCCLUSION IN CASES OF CEREBRAL ARTERIOSCLEROSIS

CASE 3.—M. B., an obese woman aged 60, was admitted to the hospital because of paralysis of her left extremities, which had developed two hours previously.

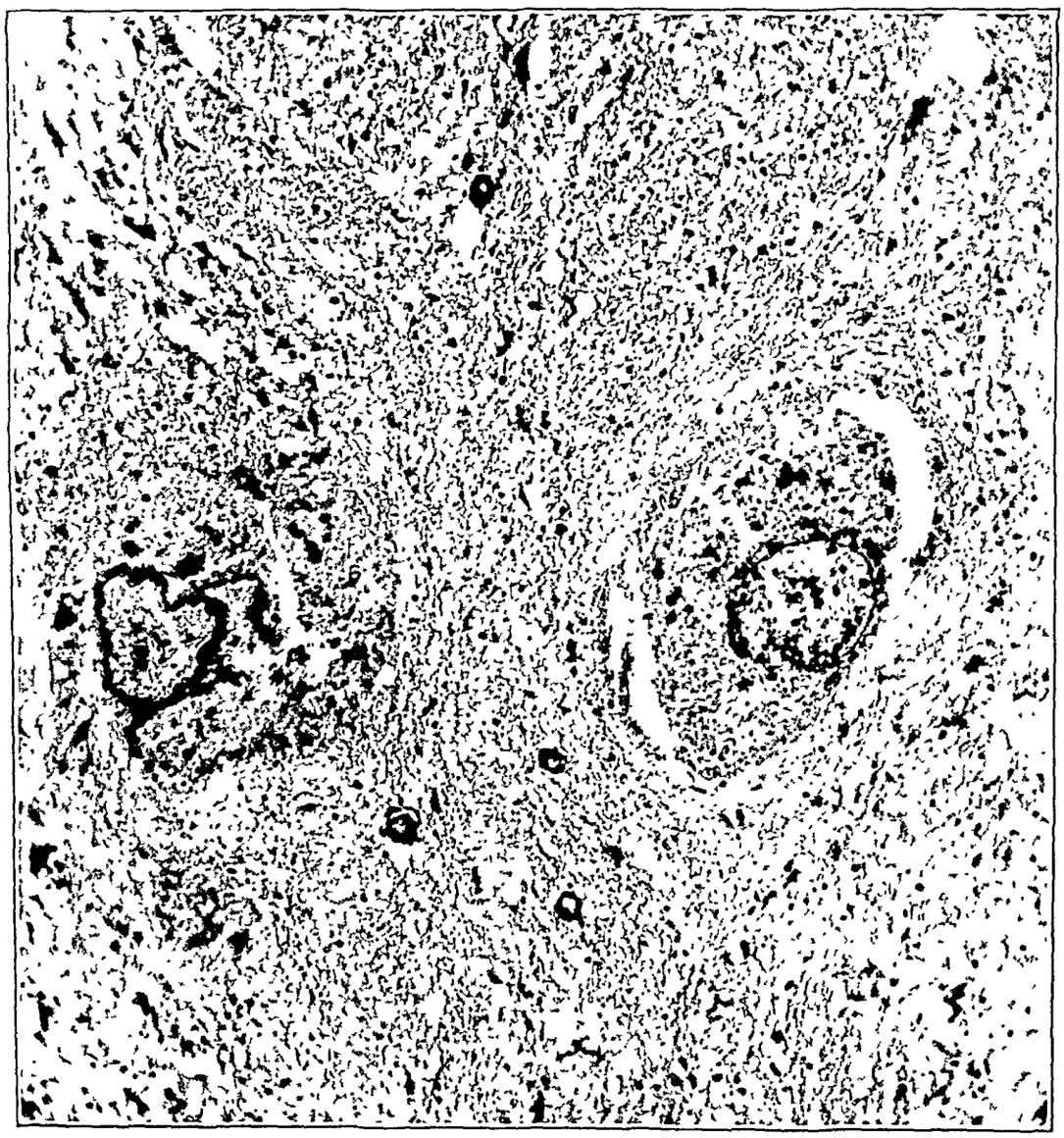

Fig. 2 (case 1).—Perivenous hemorrhage in the brain stem. Note the venous congestion and the disintegration of vessel walls. Hematoxylin-eosin stain; × 125.

Examination on admission revealed a stuporous, semicomatose condition and Cheyne-Stokes respiration. The pupils were small, equal and slightly irregular and did not react to light. There were bilateral ptosis and flaccid paralysis of the upper and lower extremities on the left side.

The cerebrospinal fluid was slightly xanthochromic, with an initial pressure of 200 mm. of water. It contained 361 red blood cells per cubic millimeter and 29 mg. of protein per hundred cubic centimeters. The Wassermann reaction was negative. The patient died two days after admission.

Necropsy revealed pulmonary edema, toxic myocardosis and cardiac hypertrophy and dilatation.

Examination of the brain disclosed a tremendous fulness of the right frontoparietal region, with evidence of softening. Inspection of the under surfaces of the brain revealed a sharp shift of the peduncles to the left, with displacement of the corpora mamillaria. The right middle cerebral artery was occluded by a thrombus, adherent to the vessel wall.

Coronal sections through the hemispheres revealed infarction of the right hemisphere in the area of distribution of the right middle cerebral artery. The entire right hemisphere was swollen and soft to touch. The right lateral ventricle was obliterated (fig. 5). There were numerous small hemorrhages in the peri-

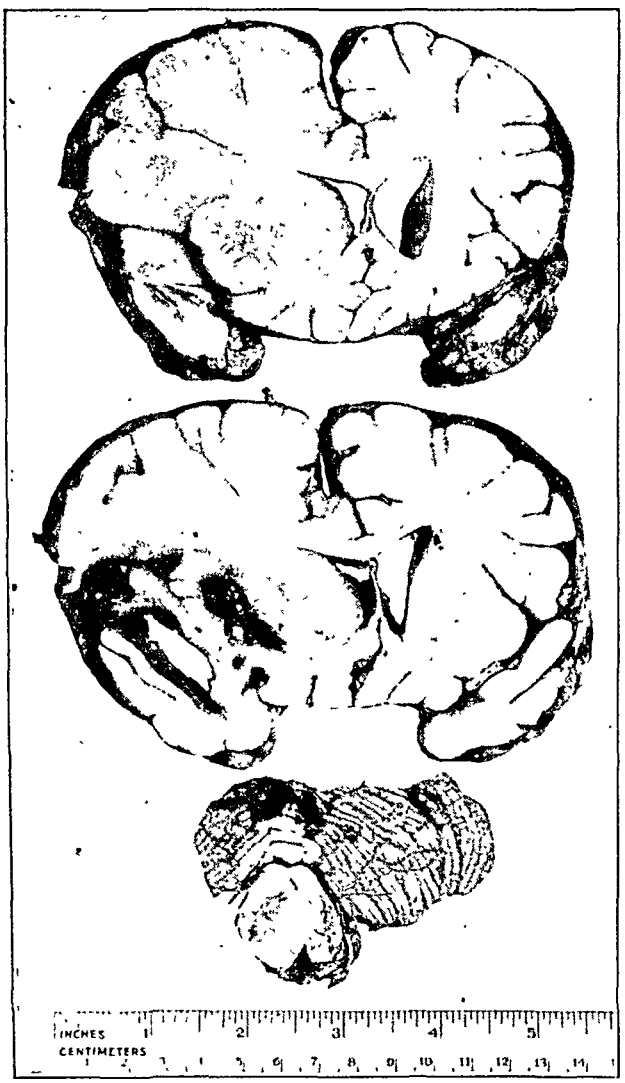

Fig. 3 (case 2).—Extensive massive hemorrhage involving the right temporoparietal region and the lateral portion of the right basal ganglia. Note the extreme swelling of the right hemisphere, associated with shift and compression of the ventricular system, and the swelling and hemorrhagic softening of the right half of the brain stem, with displacement and compression of the aqueduct of Sylvius.

aqueductal region and in the lateral portion of the left superior colliculus. The right half of the midbrain appeared broader and was somewhat soft to touch. In the pons extensive hemorrhage involved the crossing fibers and extended dorsally into the right brachium pontis.

Microscopic examination of the brain stem and pons disclosed edema and congestion. There were small hemorrhages, which, with few exceptions, were present about tremendously congested veins, the walls of which had undergone almost complete disintegration. Near the periphery of the hemorrhages were numerous congested veins and capillaries. The perivascular spaces were distended with extravasated blood and serous fluid.

B. TRAUMA

Case 4.—W. R., a man aged 56, sustained a slight laceration of the scalp when struck on the head by the hook of a traveling crane, in May 1938. Subsequently, headache of increasing intensity developed. On the morning of Aug. 24, 1938 he was admitted to the hospital, at which time neurologic examination was reported to reveal nothing significant. That afternoon, however, he became comatose. Examination then showed small, fixed pupils and rigidity of the extremities, which was more pronounced on the right side. Lumbar puncture revealed an initial pressure of 260 mm. of water. The coma deepened. Burr openings placed bilaterally in the occipital area revealed a subdural

Fig. 4 (case 2).—Loss of myelin sheaths in the swollen half of the brain stem. Note the downward displacement and compression of the left peduncular region, and the small area of necrosis, probably due to mechanical compression (Kernohan's notch) in the lateral portion of the left peduncle. Loyez stain for myelin sheaths.

hematoma on the left side, and about 50 cc. of a reddish brown fluid was released, under considerable pressure. Consciousness was not regained. The patient died on the morning of August 25.

The pertinent lesions in the brain are illustrated in figure 6. There was fulness of the entire left hemisphere. This was especially pronounced in the temporal and occipital lobes because of the presence of hemorrhagic infarction in the distribution of the left posterior cerebral artery. There resulted compression of the left lateral ventricle and shift of the midline structures to the right. Figure 6*B* illustrates the hemorrhages in the midbrain and pons.

Microscopic examination of the brain stem revealed changes similar to those described in the preceding cases.

C. SPACE-CONSUMING LESIONS

BRAIN TUMOR

CASE 5.—C. B., a man aged 44, had been well until the day of admission, when he began to talk incoherently and became disoriented.

Examination revealed inequality of the pupils, which reacted briskly to light; slight right hemiparesis, and a positive Babinski sign bilaterally.

The cerebrospinal fluid was slightly xanthochromic and was under a pressure of 200 mm. of water; it contained 20 lymphocytes and 60 red blood cells per cubic millimeter and 600 mg. of protein per hundred cubic centimeters. The Wassermann reaction was negative. The patient died thirteen hours after admission.

Fig. 5 (case 3).—Infarction of the right hemisphere in the area of distribution of the right middle cerebral artery. Note the tremendous swelling of the entire right hemisphere, with obliteration of the right lateral ventricle, and multiple hemorrhages of the brain stem.

The significant lesions of the brain are illustrated in figure 7. The left hemisphere appeared swollen. The lateral face of this hemisphere was partly destroyed by a large area of hemorrhage in the vicinity of a brownish black tumor, measuring approximately 2 cm. in diameter. The under surfaces of the frontal and temporal lobes revealed numerous brownish black, small tumor nodules. The extreme swelling of the left hemisphere resulted in compression of the left lateral ventricle and a pronounced shift of the midline structures to the right. On the left side was a well defined herniation of the uncus. Coronal sections through the midbrain revealed diffusely disseminated, small hemorrhages, especially numerous in the periaqueductal region and below the floor of the fourth ventricle (fig. 7).

Microscopic examination of the tumor revealed melanosarcoma. The histologic lesions in sections of the midbrain were essentially similar to those in the cases already described. Perivenous hemorrhages, congestion and edema were predominant features.

CASE 6.—G. O., a man aged 66, was admitted to the hospital in coma. During the preceding few years he had been treated for hypertension.

Examination disclosed right spastic hemiplegia, with weakness of the left side of the face, slight ptosis of both upper lids and equality of the pupils, both of which reacted normally to light. The fundi were normal. There was moderate stiffness of the neck. The deep reflexes could not be obtained. The Babinski sign was elicited on the right side.

The cerebrospinal fluid was clear, slightly yellow and under a pressure of 250 mm. of water; it contained 1 lymphocyte and 3 red blood cells per cubic millimeter and 188 mg. of protein per hundred cubic centimeters. The Wassermann reaction was negative.

One month later the patient died of pneumonia.

Necropsy revealed hypertensive cardiovascular disease, lobular pneumonia and congestion and toxic changes in the viscera.

Examination of the brain revealed a large, fairly well circumscribed neoplasm, measuring approximately 5 cm. in diameter, which involved the lateral portion of the left parietal lobe. The adjacent tissue immediately contiguous to the tumor was softened. The left temporal lobe showed a striking herniation of the uncus, which had resulted in displacement of the brain stem to the right. Coronal sections through both hemispheres (fig. 8) revealed tremendous swelling of the left hemisphere, with widening of the white matter and an extreme shift of the ventricular system to the right. Sections through the shifted region of the midbrain disclosed the presence of numerous small hemorrhages in the periaqueductal region and in the vicinity of the median raphe (fig. 8).

Microscopic examination of the tumor revealed a glioblastoma multiforme. Sections taken from the white matter of the left hemisphere showed a severe degree of edema and tissue liquefaction. The predominant change in sections from the brain stem consisted of tremendous congestion and engorgement of the large and small veins, associated with numerous coalescent perivenous hemorrhages.

BRAIN ABSCESS

CASE 7.—F. S., a man aged 30, was admitted to the hospital in deep coma. Four weeks prior to admission left hemiparesis developed suddenly. In the few days before his entrance to the hospital he had several focal seizures, confined to the left extremities.

Examination disclosed complete left hemiparesis, a Babinski response bilaterally and Cheyne-Stokes respiration.

The cerebrospinal fluid was clear and colorless and under a pressure of 350 mm. of water and contained 74 lymphocytes and 58 red blood cells per cubic millimeter.

Ventriculograms showed a shift of the ventricular system to the left. A bone flap was turned down in the right parietal region. When the dura was opened, purulent fluid and air were obtained. The fluid contained diplococci. The patient died two hours after operation.

The pertinent lesions in the brain are illustrated in figure 9. The right hemisphere showed striking prominence and fulness, with bulging of the precentral and postcentral gyri. This was caused by an abscess. The cavity of the abscess measured 3.3 cm. in its greatest diameter and was surrounded by a broad zone of hyperemia. The right hemisphere showed enormous swelling, which was due chiefly to edematous tissue, involving the white matter in largest part and in some areas almost completely obliterating the gray matter. The right temporal lobe showed a well defined uncal herniation, measuring 2 cm. in length and 8 mm. in width, with a clear indentation from the ipsilateral free edge of the tentorium. The right ventricle was displaced downward and was compressed. The midline structures were shifted to the left. The right thalamus appeared broader than the left. There was a small hemorrhage in the region of the left ansa lenticularis. Examination of the brain stem disclosed diffuse swelling and the presence of a small number of petechial hemorrhages.

Microscopic examination revealed the characteristic features of an abscess surrounded by a broad zone of granulation tissue. Sections taken from the white matter of the right hemisphere showed far advanced edema. The changes in the brain stem were similar to those described in the previous cases.

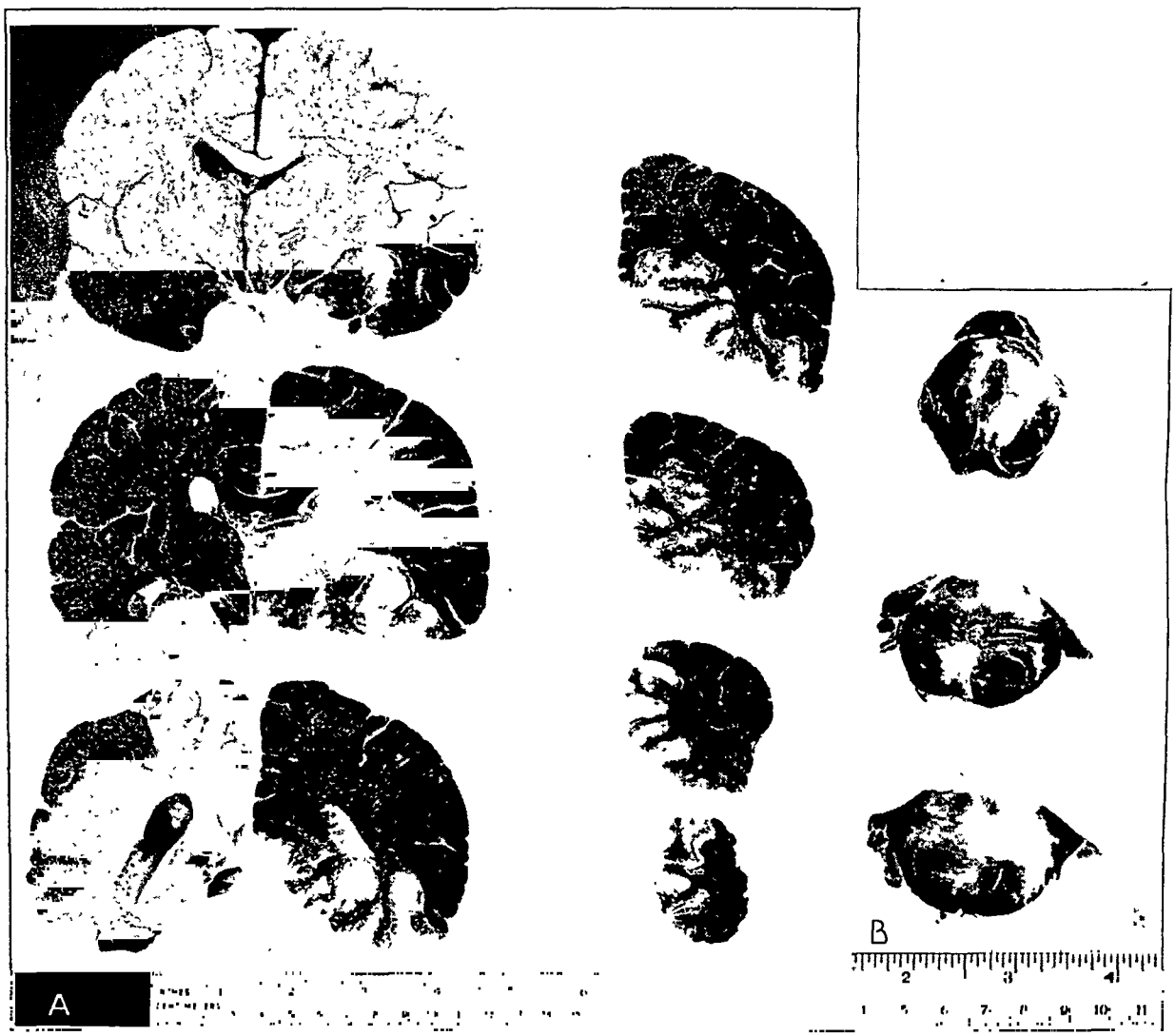

Fig. 6 (case 4).—*A*, fulness of the entire left hemisphere, associated with a post-traumatic hemorrhagic infarction in the distribution of the left posterior cerebral artery. Note the compression of the left lateral ventricle and the shift of the midline structures to the right. *B*, extensive hemorrhages in the midbrain and pons.

COMMENT

A number of significant points have emerged from this study.

Frequent Occurrence of Unilateral Cerebral Swelling and Herniation of the Brain Stem Through the Tentorial Opening.—While the mesial displacement and herniation of the hippocampal gyrus is a common observation in cases of brain tumor, as indicated by Jefferson,[2] and in cases of brain injury, as described by Evans and me,[7] its association with massive hemor-

rhages and cerebral infarctions has not been stressed. Careful analysis of the described cases revealed that in addition to the hippocampal herniation there was a frank herniation of the rostral portion of the brain stem through the tentorial opening. In all the cases cited in the present study histologic analysis of the swollen hemisphere disclosed a picture typical of cerebral edema, characterized by distention of perivascular and pericellular spaces, transudation of

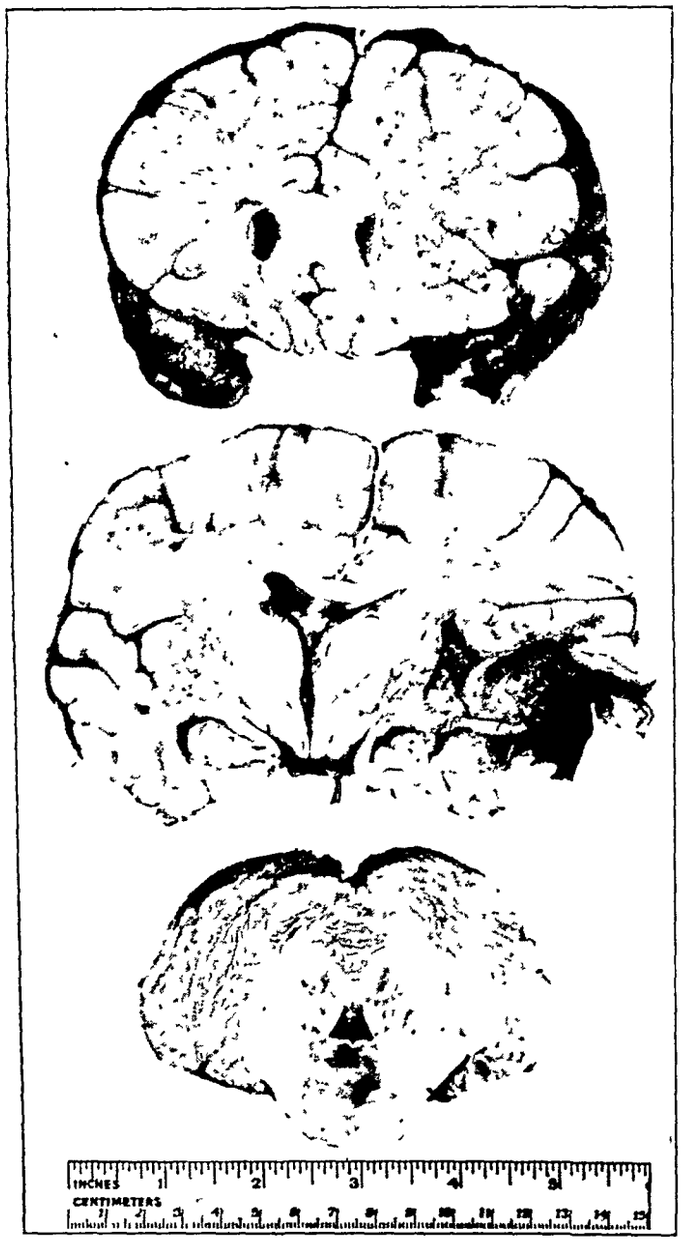

Fig. 7 (case 5).—Melanosarcoma of the left temporoparietal region, with extreme swelling of the left hemisphere and compression and shift of the ventricular system. Note the diffusely disseminated hemorrhages in the brain stem.

serum into the nerve tissue about the congested smaller blood vessels, distention of perineural spaces and an alveolar, sievelike appearance of the nerve parenchyma. The significant role of edema in the production of the herniation of the temporal uncus over the free edge of the tentorium has been emphasized in a previous paper.[7] The mechanism of the shift and compression of the ventricular system is readily explained by the unilateral swelling of the brain, sufficient in some instances even to cause displacement of the affected hemisphere across the midline under the free edge of the rigid falx. Inasmuch as the falx in the adult is a relatively immobile structure, it is obvious that there must be a tendency toward displacement of the swollen hemisphere beneath the free edge of the falx, causing herniation of the supracallosal gyrus.

In the instances of more severe edema the same side of the brain stem was observed to be swollen. Of still greater significance was the regularly observed herniation of the rostral portion of the midbrain through the tentorial opening. It is evident that as a result of the swelling of the cerebral hemisphere the mesial portion of the temporal lobe lying immediately

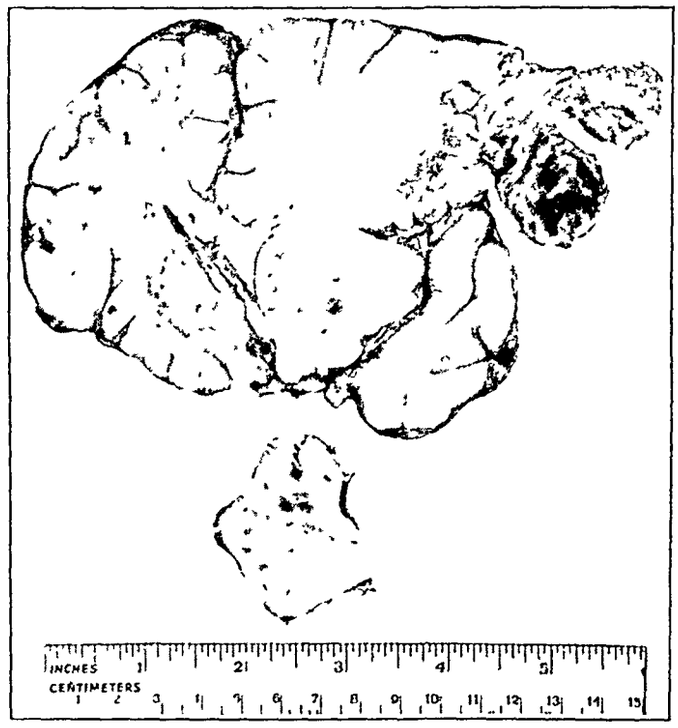

Fig. 8 (case 6).—Glioblastoma of the left parietal region, with extreme swelling of the left hemisphere and displacement of the ventricles to the right. Note the presence of numerous periaqueductal hemorrhages in the brain stem.

above the incisura tentorii was the first to be displaced downward through this incisure. With increase in the duration and severity of the edema, downward displacement and frank herniation, with distortion and compression, of the rostral portion of the midbrain take place.

Origin and Pathogenesis of Hemorrhages of the Brain Stem.—In the literature stress is laid on the arterial origin of the hemorrhages in the brain stem (Moore and Stern[4] and others). The present study indicates that they are related to the medium-sized and small veins. They were often noted in the form of narrow bands enclosing the congested veins like a sleeve, either occu-

pying the perivascular spaces or lying free in the adjacent nerve tissue. In many instances the smaller hemorrhages tended to fuse and in this way gave rise to larger hemorrhages. Only in relatively few instances, in which the hemorrhagic lesions were more extensive, was it difficult, or impossible, to be sure of the source of the hemorrhage; this was mainly because of complete disintegration of the tissue and abundance of blood. Within the large majority of the smaller hemorrhagic lesions there were recog-

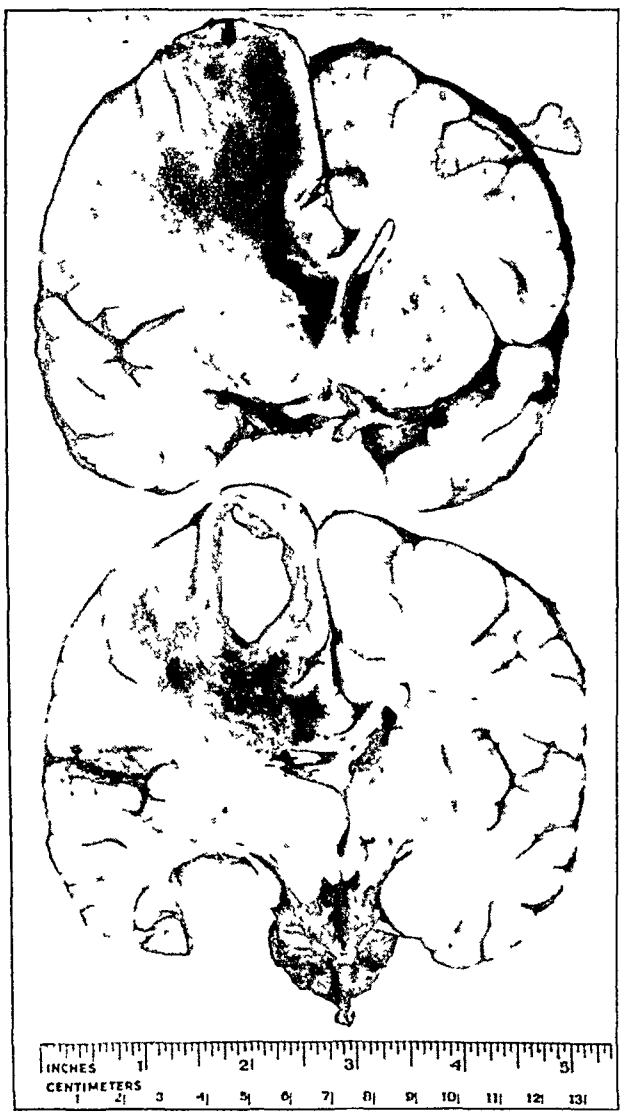

Fig. 9 (case 7).—Large abscess of the right centroparietal region, associated with swelling of the right hemisphere. Note the downward displacement of the right peduncular region and a small hemorrhage in the region of the left red nucleus.

nized as a rule one or several tremendously congested veins, with walls displaying advanced disorganization but not real rupture. In some instances the veins were represented by a mere outline of the wall (fig. 2). The latter had undergone almost complete degeneration, and the content of the vein merged with the extravasated blood surrounding the vessel. The perivascular spaces were maximally distended and filled with large masses of serous fluid and red blood cells.

Extrahemorrhagic Changes in Nerve Tissue of the Brain Stem.—The hemorrhages in the brain stem were, with few exceptions, outlined with extremely edematous tissue. This tissue was characterized by a cribriform, spongy appearance, with the formation of a large number of vacuoles, of different sizes and shapes. In some areas there was extreme liquefaction of the nerve parenchyma, characterized by a large accumulation of serous fluid with areas of complete disintegration of the nerve fibers and myelin sheaths and with evidence of degeneration of the ameboid glia cells. These changes were associated with dilatation and congestion of the smaller veins and capillaries.

Distribution of Hemorrhages in the Brain Stem.—No part of the brain stem seems to be immune from hemorrhage. Yet most of the hemorrhagic lesions were observed in the rostral portion of the brain stem; relatively few were detected in the most caudal portion of the midbrain. The majority of lesions were located in the tegmental portion of the midbrain, chiefly in the periaqueductal region. There is apparently a predisposition to hemorrhage at points where the loose texture of the extremely edematous gray matter forms a relatively poor support for the tremendously congested, thin-walled veins. This predilection of the hemorrhagic lesions for the rostral portion of the brain stem gives an important clue to the pathophysiologic mechanism of the transtentorial herniation of the brain stem which will be discussed later.

Pathophysiologic Mechanism Responsible for Herniation and Hemorrhages of the Brain Stem.—The present study has brought out the striking fact that hemorrhages of the brain stem irrespective of their origin—hypertension, arteriosclerosis, cerebral trauma, brain tumors or brain abscess—are associated with cerebral swelling and subsequent displacement of the ventricular system and herniation of the rostral portion of the mesencephalon through the incisura tentorii. The following theory of the mechanism responsible for the development of edema and hemorrhage in the brain stem is proposed for consideration: The observations recorded in this study afford evidence that a sudden increase in bulk of one of the cerebral hemispheres caused by acute edema or swelling of the brain leads to an acute increase in the supratentorial pressure. In the earlier stages the affected cerebral hemisphere displaces cerebrospinal fluid from the subarachnoidal space and from the cisterns. At a later stage the ever-increasing demand for space leads

to profound shifts of cerebral substance; the initial formation of a temporal pressure cone is followed by downward displacement and herniation of the brain stem, with subsequent plugging of the tentorial hiatus, producing a bottleneck for both the subarachnoid and the ventricular fluid. At the same time, the shifting cerebral substance may compress or occlude the narrow aqueduct of Sylvius, and the intraventricular fluid becomes trapped in the lateral and third ventricles. This leads to a steadily progressing disparity between the intracranial pressure above and that below the tentorium. With the constant increase of the intraventricular pressure the herniated portion of the brain stem is pushed deeper into the tentorial opening. As it progresses, it leads to compression and kinking of the superficial blood vessels, especially the veins, with considerable obstruction of the venous circulation and a resultant severe degree of congestion and stasis. The thin-walled, smaller veins, composed of simple endothelial tubes, are most likely to be vulnerable to compression and to anoxemic degenerative changes in their walls due to anoxemia resulting from stasis. Thus, in the earlier stages compression of thin-walled veins between the impinging uncus and the brain stem is believed to occur. In the later stages the possibility of interference with free venous outflow is even greater because the cerebral substance and the intervening veins are jammed against rigid dural reflections. This is believed to result in a severe degree of congestion and stasis, local venous hypoxia, due to the stasis, and possibly degenerative changes in the walls of the veins. Finally, if complete block of cerebrospinal fluid occurs, the smaller veins are ready to give way, and numerous perivenous extravasations take place. The small veins of the periaqueductal region are evidently poorly supported by the loose tissue of the gray substance, as compared with those of the white matter, which explains the predilection of the perivenous hemorrhages for this region. The fixation of a certain number of the larger superficial veins of the brain stem for a long distance parallel to a bony surface makes them more exposed to the increased pressure.

The anatomic observations in support of this theory of mechanism may be listed as follows: (1) the gross and histopathologic evidence of swelling or edema of the brain present in the affected hemisphere: (2) transtentorial herniation of the rostral portion of the brain stem, as observed in all cases reported in this study, and, finally, (3) the predominantly perivenous character of the hemorrhages in the midbrain associated with far advanced venous congestion and stasis.

CLINICAL OBSERVATIONS

In the past the pressure within the cerebral ventricles was considered to be always in equilibrium with the pressure throughout the spinal subarachnoid space. The observations of Hodgson [8] and Smyth and Henderson [5] give strong support to the belief that the lumbar and the ventricular pressure are not of necessity always equal. Hodgson reported a series of 49 cases of intracranial tumor in which he studied the ventricular and lumbar pressures. He concluded that partial block might result from herniation of the cerebellar tonsils and that under such conditions the initial lumbar pressure might be lower than the pressure in the ventricles. The relation between the lumbar and the ventricular cerebrospinal fluid was studied by Smyth and Henderson in a series of 39 patients, the majority of whom had intracranial tumor. Their observations proved that the ventricular pressure exceeded the lumbar pressure in all cases in which the tumor was above the tentorium and in which there was postmortem evidence of herniation of the ipsilateral temporal lobe through the incisura tentorii. On the other hand, in cases in which the tumor was situated subtentorially the lumbar and the ventricular pressure were equal. It is of interest to note that in the last group of cases there was pronounced, and in some cases extreme, tonsillar herniation. On the basis of these extremely interesting and important observations, Smyth and Henderson came to the conclusion that the disparity of the ventricular and the lumbar pressure is due mainly to herniation of the medial border of the temporal lobes into the incisura tentorii, with subsequent compression or obliteration of the iter of Sylvius.

Moore and Stern [4] collected 10 cases of hemorrhages of the brain stem in 130 cases of intracranial tumor. The presence or absence of herniation of the hippocampal gyrus was not stated in every case, but the lesion was present in the majority. In spite of this observation, the authors came to the conclusion that the hemorrhages in the brain stem "are finally brought on by reflex increase in the systemic blood pressure."

EXPERIMENTAL OBSERVATIONS

The relation between the ventricular and lumbar cerebrospinal fluid pressures has recently been studied experimentally by Kahn.[9] An ex-

8. Hodgson, J. S.: The Intracranial Pressure in Health and Disease, A. Research Nerv. & Ment. Dis., Proc. **8**:182, 1927.

9. Kahn, A. J.: Effects of Variations in Intracranial Pressure, Arch. Neurol. & Psychiat. **51**:508 (June) 1944.

treme degree of edema of the brain was produced by the perfusion of distilled water in the common carotid artery of animals. During the experiments the cisternal and the intraventricular pressure were simultaneously recorded.

A high intraventricular and a relatively low cisternal pressure were constantly observed. This disparity was interpreted as probably due to herniation of the brain stem into the foramen magnum or through the incisura tentorii, with the creation of a resulting partial block between the lateral ventricles and the cisterna magna. The circulatory and respiratory embarrassment associated with high levels of intraventricular pressure could be relieved by ventricular drainage. No circulatory or respiratory embarrassment occurred when both the cisternal and the intraventricular pressure were at high levels; medullary embarrassment appeared soon after the cisternal pressure was lowered, the intraventricular pressure alone remaining high.

CLINICAL CONCLUSIONS

What additional therapeutic conclusions are to be derived from the pathologic observations described in this study? The following significant clinical points should be stressed:

The herniation of the hippocampal gyrus, so often observed in cases of increased intracranial pressure, cannot in itself be considered responsible for the gravity and danger of the clinical syndrome. Histopathologic analysis of the reported cases revealed that most of the clinical symptoms and the frequently observed sudden death after lumbar puncture must be ascribed to the frank herniation of the rostral portion of the brain stem into the tentorial opening, followed by far advanced destruction of the brain stem.

Transtentorial herniation of the brain stem presents a grave danger and hazard for the clinician and the neurosurgeon. It is evident that lumbar puncture and pneumoencephalography must be interdicted if the existence of the herniation of the brain stem has been clinically recognized or suspected.

Transtentorial herniation of the brain stem explains in some instances the fact that lumbar pressures are not always a true index of intraventricular pressure.

Patients with lesions of the temporal lobe appear to be graver clinical risks, probably because of the possible tendency toward development of transtentorial herniation of the brain stem. Therefore, such manipulative procedures as lumbar puncture or pneumoencephalography are attended with greater risks.

It has been assumed in cases of supratentorial tumor in which death followed lumbar puncture that cerebellar herniation into the foramen magnum was responsible. However, it has not been explained how the intraventricular pressure could be transmitted to the posterior fossa. The present study indicates that transtentorial hernia of the brain stem is the important factor. The absence of formation of cerebellar pressure cone in the present group of cases corroborates my conclusions.

Clinical and pathophysiologic evidence has been accumulated to prove that the hypothalamic nuclei contain the higher regulatory centers for respiratory and cardiac control. It appears that transtentorial herniation of the brain stem might result in an interruption of the cardiorespiratory pathways between the diencephalic and the medullary centers and might be responsible for the so-called neurovegetative disturbances, namely, irregularities in respiration and pulse, hyperthermia and sudden cessation of respiration, with a rapid, bounding, and often irregular, pulse.

Attempts to release the temporal pressure cone by removal of the herniated portion of the gyrus hippocampus has been suggested by Jefferson.[2] The observations presented in this study suggest that section of the free edge of the rigid tentorium should be undertaken in an effort to distribute pressure more evenly. In many cases, particularly of tumor of the temporal lobe, this is technically possible.

It is conceivable that in certain cases the establishment of ventricular drainage might prove to be a life-saving measure, pending a more definitive operative attack.

SUMMARY

In 55 cases of transtentorial herniation of the brain stem complicating arterial hypertension, cerebral arteriosclerosis, cerebral trauma, brain tumor or brain abscess, the herniation was associated with hemorrhages and edema of the brain stem.

Hemorrhages of the brain stem are predominantly perivenous and are believed to be due to an extreme state of venous congestion, caused by compression and strangulation of the venous system draining the midbrain.

In view of the gravity of the clinical symptoms resulting from the transtentorial herniation of the brain stem, the establishment of ventricular drainage or section of the free edge of the rigid tentorium, in an effort to distribute pressure more evenly, may be a life-saving measure, pending final, and more radical, treatment.

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LIPOMA OF THE BRAIN

REPORT OF CASES

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Lipomas of the brain, because of their extreme rarity and the fact that most of them do not cause symptoms or signs during life, are clinically unimportant tumors. Most of them are unexpectedly encountered at necropsy. Up to this time the literature, as far as we could ascertain, does not contain data on any case of lipoma of the brain which was subjected to surgical attack. The chief interest in this lesion lies in its origin, and there have been a host of speculations in this regard.[1]

Lipoma of the brain has been discovered in 2 cases at the Mayo Clinic. In 1 of these cases the lesion was productive of symptoms which led to surgical removal.

REPORT OF CASES

CASE 1.—A woman student aged 18 registered at the Mayo Clinic on Jan. 17, 1933, because of attacks of unconsciousness, loss of memory and powers of concentration, and obesity.

The family history was noncontributory, and the patient had been entirely well until February 1928, when she was discovered unconscious in bed one morning. She aroused from this attack and was able to attend school that day. In June 1928 and June 1929 she had similar attacks. One day in December 1929 she ran to her father, saying she felt dizzy and faint. She promptly fell into coma but again quickly recovered. Some time during 1929 she first menstruated, and it was observed that she was gaining more weight than was considered desirable. Her memory and powers of concentration began to fail at about this time, and she had difficulty in school. In November 1932 a generalized convulsion was followed by severe headache. Early in January 1933 another attack of unconsciousness occurred. During the two years prior to her registration at the clinic she experienced intermittent frontal headaches, which disappeared after she took acetylsalicylic acid.

The patient was 63 inches (160 cm.) tall and weighed 152 pounds (68.9 Kg.). The systolic blood pressure varied between 96 and 88 mm. of mercury. The pulse rate was 60 beats per minute. There were no other general physical findings of importance. Neurologic examination revealed only a mild tremor of both hands. Examination of the eyes, including the visual fields, gave normal results. The results of routine tests on the blood and urine were within normal limits. The roentgenogram of the head (fig. 1) showed a large mass, measuring approximately 5 by 8 cm., in the midline in the frontal fossa. Calcification in its walls outlined it rather well. A diagnosis of congenital cyst with calcified walls was made.

On Jan. 23, 1933 the patient was anesthetized with ether and a long coronal incision was made back of the hair line. The scalp and periosteum were reflected from the bone in one layer, and a block of bone, measuring 12 cm. from front to back and extending 6 cm. on each side of the midline, was removed from over the frontal lobes. After the dural opening was made and the falx cerebri exposed, the right frontal lobe was retracted laterally; in the depths of the wound lay an encapsulated, fibrous, fatty mass, which extended from beneath the anterior extremity of what remained of the corpus callosum. The anterolateral limits of the tumor were reached on each side by clipping and coagulating branches of the anterior cerebral arteries and pushing the brain away from the surface of the mass. Then the anterior portion of the falx was divided, after ligation of the superior and inferior longitudinal sinuses, and the tumor was almost entirely removed together with a part of the corpus callosum. To accomplish this it was necessary to divide the left anterior cerebral artery. Several veins draining the left frontal lobe at its anterior pole were also interrupted. A mass similar to the main one, although much smaller, was removed from the choroid plexus of the left lateral ventricle. The surgical specimens are shown in figure 2.

The tumor was composed of adult adipose tissue which in some parts bore more stroma than ordinary

From the Section on Neurosurgery, Mayo Clinic.

1. (*a*) Bostroem, E., cited by Sperling and Alpers.[1g] (*b*) Ehni, G., and Love, J. G.: Intraspinal Lipomas: Report of Cases, Review of the Literature and Clinical and Pathologic Study, Arch. Neurol. & Psychiat. **53**: 1-28 (Jan.) 1945. (*c*) Gowers, W. R.: Myo-Lipoma of the Spinal Cord, Tr. Path. Soc. London **27**:19-22, 1876. (*d*) Krainer, L.: Die Hirn- und Rückenmarkslipome, Virchows Arch. f. path. Anat. **295**:107-142 (Feb.) 1935. (*e*) della Rovere, D., cited by Ritter.[11] (*f*) Scherer, E.: Ueber die pialen Lipome des Gehirns; Beitrag eines Falles von ausgedehnter meningealer Lipomatose einer Grosshirnhemisphäre bei Mikrogyrie, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:45-61 (July) 1935. (*g*) Sperling, S. J., and Alpers, B. J.: Lipoma and Osteolipoma of the Brain, J. Nerv. & Ment. Dis. **83**: 13-21 (Jan.) 1936. (*h*) Stookey, B.: Intradural Spinal Lipoma: Report of a Case and Symptoms for Ten Years in a Child Aged Eleven; Review of the Literature, Arch. Neurol. & Psychiat. **18**:16-42 (July) 1927.

adipose tissue. The fat was rather vascular, containing many small arteries and veins, but was not angiomatous. A fibrous septum separated the fat from the neural substance and sent projections into the brain substance. The small mass from the left choroid plexus was composed of adult adipose tissue which was more fibrous and cellular than ordinary fat and which lay within the plexus without any evident encapsulation by connective tissue. In certain portions of the larger tumor great quantities of small and medium-sized calcified spherules, which resembled psammoma bodies, lay in the connective tissue, and even in the brain substance bordering on the tumor (fig. 3 *a* and *b*).

After the operation the patient remained comatose; the legs were in strong extension; the arms were flexed on the chest, and static tremors occurred in all parts of the body except the head and neck. The course was progressively downhill, and she died the fifth day after operation.

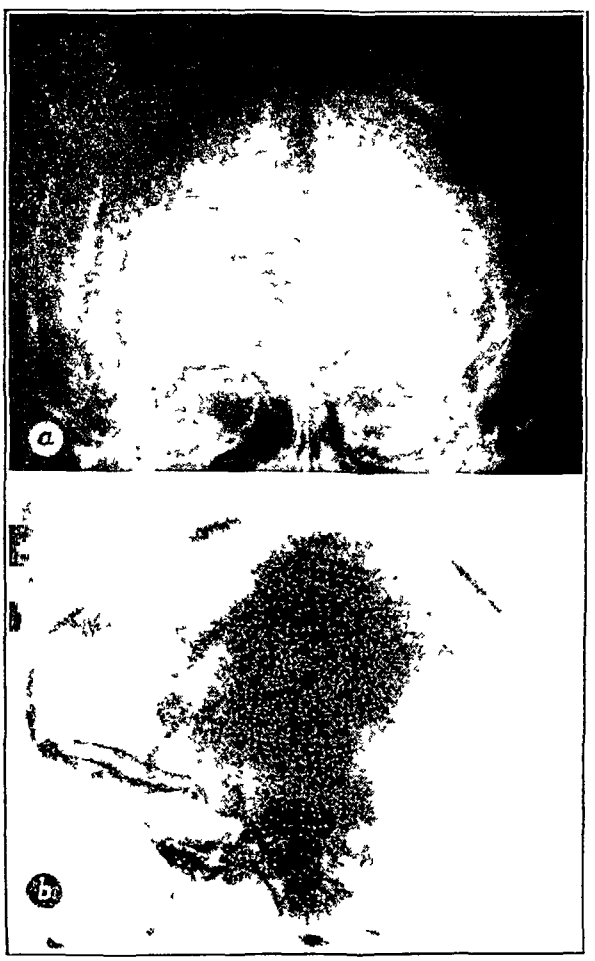

Fig. 1 (case 1).—(*a*) Posteroanterior view of the head, showing a crescentic band of calcification on each side of the midline, with the concave borders facing each other. One side is almost a mirror image of the other. (*b*) Lateral view of the head, showing a broad, angular band of calcification lying in the general position of the rostrum of the corpus callosum.

Necropsy revealed infarction of the left frontal lobe, with thrombosis of the veins over the surface. The superior longitudinal sinus was patent posterior to the point of ligature. A cavity, measuring 4 by 4 by 5 cm., lay beneath the site from which the rostrum of the corpus callosum was removed This cavity communicated with the lateral and third ventricle. Remnants of the tumor remained in the walls. Otherwise nothing of significance was noted.

Case 2.—A girl aged 16 years registered at the Mayo Clinic on March 10, 1937, complaining of headaches, vomiting, vertigo and drowsiness.

The family history was noncontributory, and the patient had been perfectly well until December 1936, when she began to have occasional headaches in the morning; these lasted from a few hours to all day. They were usually frontal and had not been severe until the month prior to her registration. On March 3, 1937 she discontinued attendance at school because of the headaches. The next day vertigo developed. On March 5 she vomited and thereafter continued to do so three or four times a day. On March 6 the headache became worse and extended to the suboccipital and cervical region. The pain was even felt down to the left arm. On March 7 she noticed tinnitus and staggering to the left in walking. On March 8 she was hospitalized in her home town but two days later was brought to the clinic, when paralysis of the extraocular muscles and drowsiness set in.

Fig. 2 (case 1).—Tissue removed at operation.

On her admission to the clinic the patient was drowsy but cooperative and was obviously extremely ill. The significant findings were mild horizontal nystagmus, bilateral papilledema of 3 D., bilateral paralysis of the oculomotor and facial nerves, dysarthria, incoordination of the left arm, stiff neck and a moderately strong Kernig sign on both sides. Sensation was normal; there were no signs referable to the pyramidal tract, and the visual fields were grossly normal. The urine contained a moderate amount of albumin, a moderate number of pus cells and some erythrocytes. The concentration of urea was 20 mg. per hundred cubic centimeters of blood. The leukocytes numbered 16,600 per cubic millimeter of blood, and the hemoglobin measured 14 Gm. per hundred cubic centimeters of blood Roentgenograms of the head and chest revealed nothing abnormal.

On the day after her registration the systolic blood pressure gradually rose and the patient became less and less responsive. The next day she was comatose, the temperature rose to 102 F., and she died.

Necropsy disclosed an extensive carcinomatous change throughout the mucosa of the stomach. This organ was studded with small nodules, measuring from 2 to

5 mm. in diameter, composed of malignant, mucus-containing, signet ring cells. Metastatic lesions were observed in the liver, spleen, colon, periadrenal fat, renal pelves, bladder, vagina, cervix, ovaries, mesenteric nodes, thymus, epicardium, lungs, hilar nodes of the lungs, thyroid, axillary nodes and cerebral meninges and in a small lipoma lying on the corpus callosum. This lipoma, which was 3 cm. long and from 5 to 8 mm. in diameter, lay on the posterior half of the corpus callosum. It had no firm attachments to the gyri cinguli or the corpus callosum (fig 4 *a* and *b*) and was too small to be of any consequence.

COMMENT

Of most importance in case 1 was the fact that the lesion was mistaken for a cystic tumor with calcified walls. Because of this error the roentgenograms were examined again. They showed a thick calcified layer in both the postero-anterior and the lateral exposure. The lateral view seemed to provide a profile of the rostrum of the corpus callosum. The thick calcified layer differed considerably from the fine line of calcium observable in the roentgenogram in cases of craniopharyngioma and may be a basis for future differentiation.

With a tumor of such size and in such a complex location it is impossible to say from what the lesion arose—whether from the corpus callosum, the lamina terminalis, the choroid plexus or some other structure. To be safe, we have classified the tumor as originating in the choroid plexus or the ventricular wall, although it may have come from the rostrum of the corpus callosum.

In case 2 the features which concerned the lipoma were not extraordinary. It is inconceivable that the lipoma and the carcinoma of the stomach were related, though this combination has been remarked on by others.[1e]

The subject of lipoma of the brain has been reviewed a number of times, but most recently by Krainer.[1d] This author was able to study reports of 56 cases of such tumors. The cases in his tables total 57, but he duplicated the case of Chouppe [2] by listing it as no. 25 and again as no. 50. To these 56 cases should be added a number of other cases in order to bring the total up to date. The cases of Weber and Daser,[3] Scherer,[1f] Baker and Adams,[4] Sperling and

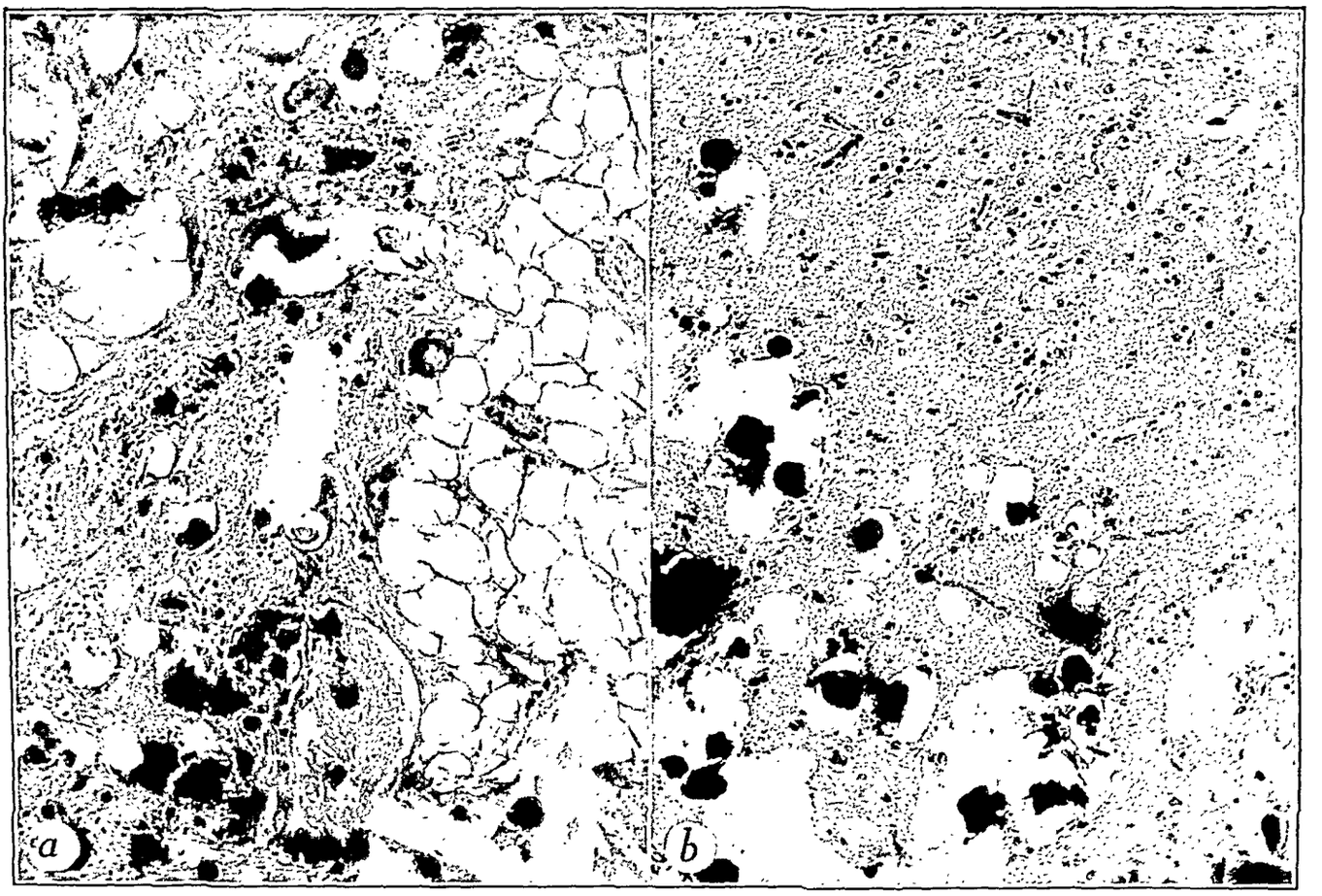

Fig. 3 (case 1).—(*a*) Portion of the fibrous capsule of the larger tumor. The adult adipose tissue is bordered by a heavy capsule of collagen, which contains islands of fat cells and numerous lamellated calcified bodies. (*b*) Portion of the brain bordering the tumor. Numerous calcified bodies are lying in the neural substance, without any surrounding fibrous tissue. Hematoxylin and eosin stain; × 85.

2. Cited by von Sury.[6]

3. Weber, F. P., and Daser, P.: Osteo-Lipoma of the Brain Arising from the Infundibulum, Tr. Path. Soc. London **58**:219-225, 1907.

4. Baker, A. B., and Adams, J. M.: Lipomatosis of the Central Nervous System, Am. J. Cancer **34**: 214-219 (Oct.) 1938.

Alpers [1g] and Rubinstein [5] are genuine instances of this lesion and may be added without argument. According to von Sury,[6] Rokitansky [2] described a case in addition to the one accepted by Krainer, and there seems no good reason for not including this case in the total. Misch [7] reported 2 cases of intracranial lipoma, but only in the second was the tumor intradural, probably originating in the pia. This case should be added to the total. Scherer [1f] referred to cases described by Simon,[8] but all that can be learned is that Simon reported 2 cases of lipoma of the clivus and 1 case of lipoma of the plexus. Whether the 2 lipomas of the clivus were extradural, as was the tumor in the first case reported by Misch, can only be surmised, but the remaining case is probably pertinent to the present discussion. Krainer merely listed 5 additional cases, which he was unable to study but which were evidently accepted by others.[9] He did not include the case reported by Shaw [10] because he considered the lesion to be extradural. Shaw stated that the tumor was in the meninges, and in his anatomic description he related the mass to the bony structures of the middle fossa rather than to the brain. It seems that when the brain was removed the tumor was left behind. Sperling and Alpers [1g] accepted Shaw's case as genuine. Without the case of Shaw or the 2 cases of tumor of the clivus reported by Simon the total number is 69.

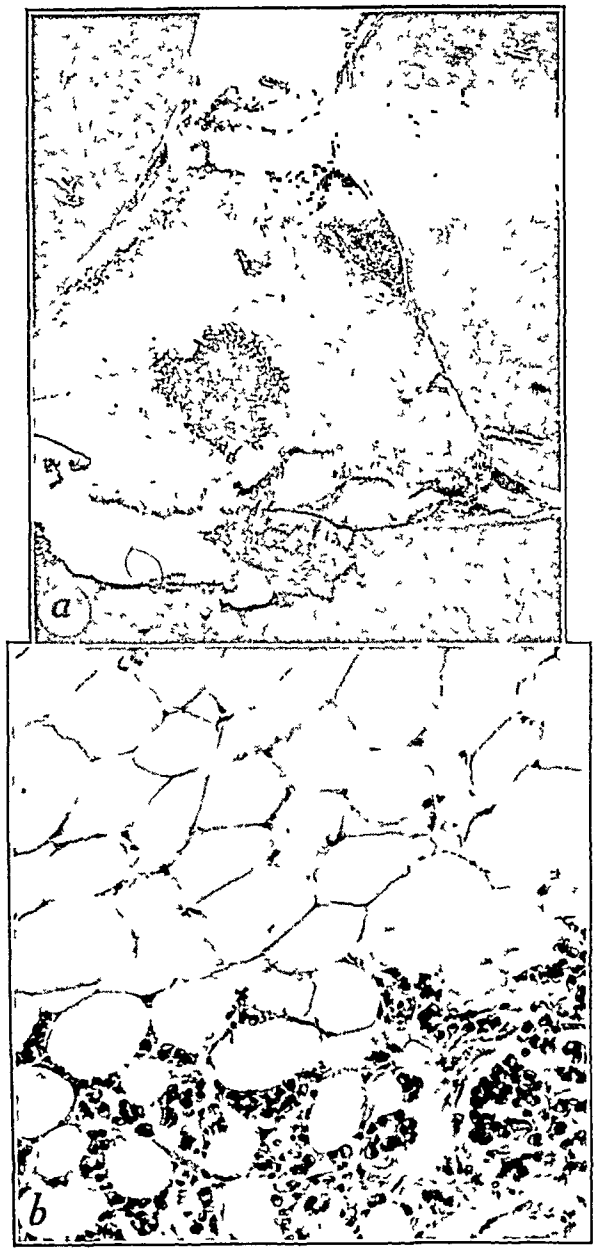

Fig. 4 (case 2).—Tissue from the lipoma: (*a*) Section through the entire lipoma (× 9). The corpus callosum lies below, and to either side are the gyri cinguli. In the center of the lipoma and at the upper right aspect are carcinomatous nodules metastatic from the stomach. The origin appears to be from the dorsal surface of the corpus callosum, but smaller islands of carcinomatous cells and an artefactitious separation obscure the point of origin. (*b*) Portion from the center of the lipoma, showing the adult adipose tissue above and the edge of the carcinomatous nodule below (× 135). The eccentric position of the nuclei in the mucus-containing, signet ring cells in the metastatic lesion from the stomach may be noted. Hematoxylin and eosin stain.

Sperling and Alpers arrived at a total of 74 cases before reports of the cases of Baker and Adams,[1] Scherer,[1f] Krainer,[1d] Misch [7] and Simon[8] were available. To arrive at their figure, they augmented Verga's list.[1a] Certain of the cases added to Verga's list by Sperling and Alpers should be omitted. The cases of Ritter [11] and Oppenheim and Borchardt [12] were primarily instances of lipoma of the spinal cord and have been properly classified in reports on this lesion. The case of "Verfasser" is in reality von Sury's [6] own case, duplicated by a curious error on the part of Sperling and Alpers. Von Sury used the word *Verfasser* ("author") in his tabulations to refer to the case he had just reported, and Sperling and Alpers evidently accepted the

5. Rubinstein, B. G.: Ueber einen Fall von unvollständig fehlendem und durch Fettgewebe ersetztem Balken, Frankfurt. Ztschr. f. Path. **44**:379-386, 1932.

6. von Sury, K.: Ein gemischtes Lipom auf der Oberflache des hypoplastischen Balkens, Frankfurt. Ztschr. f. Path. **1**:484-491, 1907.

7. Misch, W.: Meningeal Lipomas in the Foramen Magnum, J. Neurol. & Psychopath. **16**:123-129 (Oct) 1935.

8. Simon, cited by Scherer.[1f]

9. Footnotes 1*a* and 6.

10. Shaw, R. H.: Ptosis Produced by Intracranial Lipoma, Brit. M. J. **2**:1828 (Dec. 26) 1896.

11. Ritter, A.: Ein Lipom der Meningen des Cervicalmarks, Deutsche Ztschr. f. Chir. **152**:189-209, 1920

12. Oppenheim, H., and Borchardt, M.: Weiterer Beitrag zur Erkennung und Behandlung der Rückenmarksgeschwulste, Deutsche Ztschr. f. Nervenh. **60**: 1-32, 1918.

word as the name of an additional author. In Virchow's [13] case a dural tumor of some sort was present, but it was not a pial or a ventricular tumor, and therefore we did not include it in our total.

Haverfield and Walker [14] have reported a type of tumor which we rigidly exclude from classification with pial lipomas. Although these authors stated that their tumor and other lipomatous meningiomas do not differ from the lipoma outside the central nervous system, our opinion is to the contrary, and the histologic study of their own tumor contradicts them. They reported that portions of their tumor were composed of meningotheliomatous cells—certainly not to be found in the ordinary lipoma. We have had experience with meningiomas of this sort and though many of the cells may be fatty, even to the point of resembling the cells of adult adipose tissue, the true nature of the tumor is indicated by the presence of sheets of nonadipose cells and whorl-like formations. The most striking gross distinction between fatty meningioma and true lipoma is the lack of dural attachment in the lipoma. True lipoma of the nervous system is similar to lipomas outside the nervous system except that it frequently displays calcification, or even bone.

The 69 cases we found in our partial review of the literature and the 2 cases reported in this communication bring the total to 71 reported cases. Krainer chose to relate the tumors he studied to the various intracranial cerebrospinal fluid cisterns. Though this method of investigation was pertinent to the development of his thesis, the problem seems clearer to us if 70 of the tumors are tabulated according to the structure from which they arose, with the following result: Twenty-five arose from the corpus callosum; 18, from the ventral diencephalic structures; 9, from the choroid plexus or the walls of the lateral and third ventricles; 7, from the dorsal portion of the midbrain; 1, from the ventral portion of the midbrain; 4, from the medulla; 4, from the pons and structures of the cerebellopontile angle, and 2, from the cerebral convexities. Six of the tumors which arose from the corpus callosum were accompanied by one or more additional tumors of the choroid plexus, and 1 was accompanied by a tumor of the olfactory nerve.

13. Virchow, R.: Ein Fall von bösartigen, zum Theil in der Form des Neuroms auftretenden Fettgeschwülsten, Virchows Arch. f. path. Anat. **11**:281-288 (March) 1857.

14. Haverfield, W. T., and Walker, A. E.: Lipoblastic Meningioma, Arch. Surg. **42**:371-378 (Feb.) 1941.

One of us, with Love,[1b] has discussed in some detail the problem of the origin of lipoma of the pia mater in connection with intraspinal lipoma; since the problem which concerns lipoma of the brain is the same, it will be adequate merely to list the various mechanisms suggested to account for such a fatty mass. They are: (1) proliferation of the few fat cells normally present in the leptomeninges; (2) deposition of fat in cellular masses arising from proliferation of common connective tissue cells; (3) deposition in connective tissue or glia of fatty products of the breakdown of nerve tissue; (4) fatty degeneration of proliferated glia; (5) abnormal inclusion of fat-forming material within the closing lips of the neural groove, and (6) perverted differentiation of persisting embryonic meninx.

Scherer amplified the last-mentioned mechanism by indicating the probable primitive cells responsible for the formation of the fat—an adaptation of Wassermann's [15] researches. One of us, with Love,[1b] has further amplified this mechanism by suggesting that the primitive cells with fat-forming potentialities are permitted to form fatty masses by a defect in the neural crest. This fundamental defect results in failure of local control of formation of fat, and the stage is set for the lipoma to develop.

The gross and microscopic features of pial lipoma are not significantly different from those of lipoma in other locations except that intracranial lipoma may contain calcified material ranging from psammoma bodies to true bone. In case 1 of this report calcification was present even in the brain substance adjacent to the tumor. The significance of this observation is unknown. An intraspinal pial lipoma containing calcium has not been discovered.[1b]

The clinical importance of the intracranial pial lipoma remains slight even with the demonstration that a tumor of this type may produce symptoms, give roentgenographic evidence of a confusing nature and be subjected to removal. The lesion is merely to be remembered in the differentiation of calcified tumors of the brain.

SUMMARY AND CONCLUSIONS

In 1 of 2 cases of lipoma of the brain described in this paper the tumor caused symptoms of brain tumor, contained enough calcium to cast a shadow in the roentgenogram and was removed surgically.

15. Wassermann, F.: Die Fettorgane des Menschen. Entwicklung, Bau und systematische Stellung des sogenannten Fettgewebes, Ztschr. f. Zellforsch. u. mikr. Anat. **3**:235-328, 1926.

With the 2 cases reported in this paper, 71 cases of lipoma of the brain or intradural cranial nerves have been reported in the literature. The favored sites of origin, in their order of frequency, are the corpus callosum, the ventral diencephalic structures, the choroid plexus or ventricular walls of the lateral and third ventricles and the dorsal surface of the midbrain.

The mechanism of formation of this lipoma is probably a perversion of differentiation of the primitive meninges. Elements with fat-forming potentialities are present in the meninges, and the lipoma develops when the ectodermal mesenchyme contributing to the leptomeninges is defective.

This tumor has slight clinical importance, but it must be added to the list of lesions requiring differentiation when calcium is discovered on roentgenologic examination.

The Mayo Clinic.

BROMINE CONTENT OF THE BLOOD IN MENTAL DISEASES

I. DEMENTIA PRECOX

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AND THEODORE R. MARVIN, M.D.
COLUMBUS, OHIO

Bromide therapy has been used for many years in the treatment of conditions associated with psychomotor disturbance and increased vasomotor irritability. From time to time the bromide content of the blood of patients with such disorders has aroused the interest of investigators. In 1931 Zondek and Bier [1] reported that in 29 of 34 patients with manic-depressive psychoses who were examined the bromine content of the blood was from 40 to 60 per cent below the normal value (1 mg. per hundred cubic centimeters) previously established by them. The average value for the 34 patients was 0.572 mg. per hundred cubic centimeters. They also stated that in 5 out of 17 patients with schizophrenia studied the blood bromides were low. In 1933 the same authors [2] concluded that the bromide content of the blood of patients with mental disease was likely to be low and discussed the concentration for 6 mentally depressed patients.

Klimke and Holthaus [3] presented the cases of 6 patients with psychomotor disturbances and concluded that lowering of the blood bromides was characteristic and proportional to the intensity of the disturbance. Sacristan and Peraiata [4] analyzed the blood of 13 women with manic-depressive psychoses and in every case found the bromine content to be less than the accepted normal. Ten women with other psychoses were also studied, but no deviation from normal values for blood bromide was noted. On the basis of these results, these investigators concluded that the bromide concentration of the blood was lowered in patients with manic-depressive insanity. Since all these investigators had used methods which were later shown to be unreliable, the validity of their conclusions is open to question.

In 1933 Hennelly and Yates,[5] using a new and more accurate method of analysis of their own, obtained low values for the bromine of the blood for males with schizophrenia of all types, paraphrenia, manic-depressive psychoses and involutional melancholia, while the values for patients with psychoneuroses and organic dementia were within the normal range. These investigators placed little reliance on the estimation of the bromine content of the blood in the diagnosis of manic-depressive psychosis, since no correlation between the stage of the mental disease and variation in the bromine content of the blood could be obtained. These observations were based on the study of 56 patients, including 11 mentally normal patients, as well as the patients with mental disease noted.

Meier and Schlientz [6] used the method of Leipert for the analysis of blood bromides for 35 patients with psychoses. For 27 patients with nonbromide medication the bromine content ranged from 75 to 233 micrograms per hundred cubic centimeters, with an average value of 132 micrograms. Pierre and Camille Chatagnon,[7] also reporting in 1936, stated that for 23 of 31 patients with manic-depressive psychosis which they had studied the bromine values were higher than normal.

Because of the unreliability of the methods used by some of the previous investigators, and because of the few cases of any one type of mental condition included in the reports of any of these workers, we decided to make an extensive study of the bromine content of the blood of various types of mentally disturbed patients. The first investigation was restricted to patients with dementia precox. The subjects chosen had all

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The present investigation was made possible through the staff of the Columbus State Hospital for the Insane, Dr. J. F. Bateman, Superintendent.

1. Zondek, H., and Bier, A.: Brom im Blute bei manisch-depressivem Irresein, Biochem. Ztschr. **241**: 491, 1931.

2. Zondek, H., and Bier, A.: Brom in Blute bei Psychosen, Klin. Wchnschr. **12**:55, 1933.

3. Klimke, W., and Holthaus, B.: Ueber den Bromspiegel des Blutes bei psychomotorischen Erregungszuständen, Deutsche med. Wchnschr. **58**:1558, 1932.

4. Sacristan, J. M., and Peraiata, M.: Ueber den Bromspiegel des Blutes bei manisch-depressivem Irresein, Klin. Wchnschr. **12**:467, 1933.

5. Hennelly, T. J., and Yates, E. D.: Blood Bromine in the Psychoses, J. Ment. Sc. **81**:173, 1935.

6. Meier, C. A., and Schlientz, W.: Neure Untersuchungen über den Bromspiegel im Blut bei Psychosen, Klin. Wchnschr. **15**:1845, 1936.

7. Chatagnon, P., and Chatagnon, C.: Le métabolism du brome dans l'organism humain, Compt. rend. Acad. d. sc. **202**:1119, 1936.

been inmates of the Columbus State Hospital for the Insane for more than three months, while some had been in residence there for more than ten years.

A method of bromine analysis previously devised by one of us (H. L. W.)[8] was used in this investigation. The accompanying table gives the results for 172 patients with dementia precox.

Although the values in the table range from 0.09 to 1.60 mg. of bromine per hundred cubic centimeters of whole blood, nevertheless the values in few cases approached these limits. The figures for 80 per cent of the subjects differing from this value by less than 0.2 mg. per hundred cubic centimeters. The bromine content of the blood of patients with dementia precox included in the present study therefore appears to be consistently lower than that of normal healthy persons residing in the same geographic area. Differences in blood bromine content of the two groups cannot be attributed entirely to differences in bromide intake in food or water, since the same sources were available to the two groups.

Bromine Content of the Blood of One Hundred and Seventy-Two Patients with Dementia Precox

Case No.	Age, Yr.	Bromine per 100 Cc. Whole Blood	Case No.	Age, Yr.	Bromine per 100 Cc. Whole Blood	Case No.	Age, Yr.	Bromine per 100 Cc. Whole Blood	Case No.	Age, Yr.	Bromine per 100 Cc. Whole Blood
Males			Males			Males			Males		
1	62	0.55	45	37	0.56	89	24	0.49	133	22	0.56
2	60	0.45	46	25	0.36	90	59	0.52	134	59	0.69
3	63	0.58	47	57	0.77	91	40	0.47	135	39	0.40
4	65	0.41	48	35	0.50	92	45	0.62	136	39	0.69
5	75	0.77	49	32	0.38	93	59	0.54	137	24	0.68
6	54	1.00	50	30	0.79	94	55	0.51	138	34	0.68
7	61	0.72	51	34	0.54	95	28	0.56	139	66	0.76
8	77	0.69	52	33	0.42	96	50	0.59	140	50	0.75
9	40	0.56	53	33	0.46	97	27	0.65	141	56	0.48
10	59	0.73	54	35	0.09	98	34	0.52	142	31	0.64
11	48	0.71	55	32	0.56	99	37	0.47	143	35	0.69
12	62	0.59	56	32	0.59	100	37	0.50	144	22	0.47
13	58	0.79	57	32	0.54	101	31	0.60	145	29	0.58
14	55	0.69	58	34	0.38	102	40	0.36	146	64	0.57
15	49	0.43	59	36	0.32	103	33	0.79			
16	45	0.53	60	40	0.56	104	29	0.23			
17	56	0.75	61	62	0.29	105	37	0.67	Females		
18	59	0.69	62	27	0.60	106	52	0.57			
19	46	0.67	63	36	0.55	107	23	0.72	1	62	1.00
20	53	0.36	64	27	1.00	108	44	0.37	2	40	0.50
21	57	0.49	65	47	0.70	109	27	0.45	3	50	0.69
22	47	0.73	66	75	0.70	110	59	0.14	4	32	0.33
23	45	0.59	67	47	0.73	111	29	0.65	5	42	0.56
24	70	0.50	68	30	0.66	112	20	0.54	6	26	0.33
25	50	0.48	69	19	0.39	113	17	0.45	7	35	0.42
26	56	0.63	70	37	0.60	114	31	0.43	8	36	0.35
27	47	0.52	71	46	0.71	115	42	0.79	9	33	0.45
28	49	0.76	72	46	0.79	116	21	1.60	10	34	0.36
29	57	0.18	73	32	0.44	117	37	0.68	11	38	0.93
30	42	0.42	74	30	0.69	118	27	0.58	12	43	0.41
31	62	0.45	75	66	0.45	119	39	0.59	13	25	0.37
32	61	0.57	76	30	0.60	120	34	0.45	14	50	0.81
33	40	0.46	77	32	0.59	121	25	0.38	15	58	0.42
34	34	0.42	78	26	0.68	122	28	0.59	16	27	0.41
35	56	0.59	79	35	0.42	123	36	0.22	17	29	0.51
36	36	0.52	80	46	0.68	124	37	0.71	18	33	0.42
37	37	0.56	81	34	0.79	125	31	0.64	19	29	0.40
38	53	0.73	82	59	0.56	126	21	0.26	20	40	0.42
39	36	0.56	83	31	0.85	127	33	0.34	21	35	0.49
40	68	0.16	84	66	0.69	128	23	0.37	22	51	0.35
41	59	0.77	85	31	0.36	129	28	0.54	23	21	0.45
42	47	0.47	86	51	0.70	130	59	0.89	24	31	0.32
43	46	0.43	87	27	0.59	131	29	0.69	25	14	0.41
44	34	0.67	88	38	0.75	132	59	0.69	26	41	0.35

values for 64 patients (37.2 per cent) differed from the average value (0.555 mg. of bromine per hundred cubic centimeters) by less than 0.1 mg., while the values for 138 patients (80.2 per cent) were within 0.2 mg. of the average.

A previous study[9] of the bromine content of the blood of normal healthy persons residing in Columbus revealed an average value of 0.81 mg. of bromine per hundred cubic centimeters, with

8. Wikoff, H. L.; Bame, E., and Brandt, M.: A Method for the Determination of Bromine in a Protein-Free Filtrate, J. Lab. & Clin. Med. **24**:427, 1939.

9. Wikoff, H. L.; Brunner, R. A., and Allison, H. W.: The Normal Bromine Content of the Blood of Healthy Individuals, Am. J. Clin. Path. **10**:234, 1940.

SUMMARY

The average bromine content of the blood of 172 patients with dementia precox was found to be 0.555 mg. of bromine per hundred cubic centimeters of blood. It is significant that the values for 80.2 per cent of the patients examined varied from the average (0.555 mg.) by less than 0.2 mg. The average value for the patients with dementia precox was lower than the average obtained by the same method for normal persons residing in the same city.

Drs. Rothermich, Michael and Whittenbrook selected the patients and furnished the diagnoses for this study.

Ohio State University College of Medicine.

SKULL DEFECT AND HERNIATION OF CEREBRUM WITH ABSENCE OF DURA FOLLOWING HEAD INJURY IN ADOLESCENCE

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AND
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A few cases of delayed absorption in bones of the skull following head injury have been described. Pancoast, Pendergrass and Schaeffer [1] reported a case in which an unusual alteration in bony structure developed after a fracture of the skull, with hernia of the cerebrum and elevation of a fragment of bone from the cranium. Rowbotham [2] described a defect in the vault of the skull with traumatic malacia or absorption of bone following a closed head injury. The thinning and scalloping of bone adjacent to a comminuted fracture of the skull, characteristic of traumatic cyst of the leptomeninges, is not unusual. It was well portrayed by Dyke [3] and has been duplicated in our series of head injuries. However, in a review of the literature we have been able to find no instance of a defect in the inner table of the skull alone with herniation of the brain and absence of dura mater following head injury. Having encountered such a case, we present it as an aid in the differentiation of lesions of this type from tumors and infections of the skull.

REPORT OF A CASE

History—A private in the Women's Army Corps, aged 32, was admitted to the Walter Reed General Hospital on Feb. 10, 1944, as a transfer from the station hospital at Fort George G. Meade, Md., because of headache, fainting spells and the presence of an irregular area of destruction of bone in the left parietal area of the skull.

She stated that at the age of 15 (in 1927), while walking along a country road one evening, she had been knocked down by a passing automobile, which struck the left side of her head. She was unconscious for twenty or thirty minutes. She received medical care and was kept in bed for two weeks, but no roentgenograms of the skull were taken. Except for mild, transient frontal headaches, she was well after the accident until 1939. During that year headaches, which were not lateralized and not accompanied by vomiting, became more severe and recurred two or three times a month, each attack lasting about twelve hours. Under a regimen of rest the attacks subsided again, only to recur in 1943, after she had enlisted in the Women's Army Corps. In November 1943, one month after enlistment, she felt dizzy one day while marching to a class and fainted on reaching the school where the classes were held. She did not have a convulsion and was unconscious for only five minutes. Later in the same month, while drilling one day, she fainted again, and she had two similar episodes on Jan. 17 and Jan. 18, 1944, without convulsive movements, biting of the tongue or incontinence. Examination at the Fort George G. Meade Station Hospital revealed only an equivocal Babinski sign on the right side. Because of the finding of an irregular defect in the left parietal bone, however, she was transferred to the Walter Reed General Hospital for further study, arriving there on February 10.

Examination.—Physical examination on admission to the hospital revealed no evidence of acute disease. There was slight tenderness over the left parietal area of the skull on tapping or pressure. The blood pressure was 110 systolic and 76 diastolic. General physical examination revealed nothing abnormal except for a small mass in each pelvic vault. Neurologic examination showed no significant abnormalities.

Roentgenograms of the skull revealed an area of moth-eaten destruction in the left parietal bone, beginning close to the sagittal suture line and extending laterally in the midparietal area for a distance of about 7 cm. (figure, *A*). The anteroposterior diameter was about 4.5 cm., and in the posteroanterior projection the volume of the skull seemed larger on the left side. The inner table alone appeared involved in the diffuse destructive process. There was no increased vascularity in the surrounding bone and no definite involvement of the scalp. The roentgenographic impression was that of cholesteatoma of the left parietal bone. Roentgenograms of the long bones, the pelvis and the thoracic cage showed no abnormalities.

An electroencephalogram recorded a dominant rhythm of 10 per second. There were no seizure discharges and no evidence of a focal lesion. Overventilation pro-

From the Neurosurgical Section, Walter Reed General Hospital, Washington, D. C.

1. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1940.

2. Rowbotham, G. F.: Acute Injuries of the Head, Edinburgh, E. & S. Livingstone, 1942.

3. Dyke, C. G.: The Roentgenological Aspects of Fracture of the Skull and Injuries to the Brain, in Brock, S.: Injuries of Skull, Brain and Spinal Cord, ed. 2, Baltimore, Williams & Wilkins Company, 1943.

duced no increased frequency of potentials. The impression was that of a normal electroencephalogram. A spinal puncture showed normal pressure, no cells and a total protein of 25 mg. per hundred cubic centimeters.

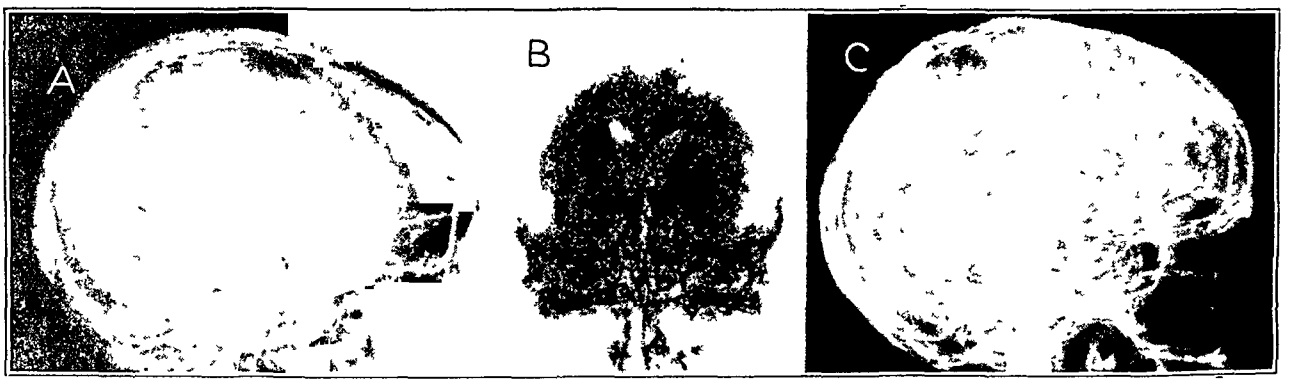
Operation.—On February 22, with the patient under ether anesthesia administered intratracheally, a small flap was marked out on the left parietal region of the scalp, with its base along the midline. A small linear scar, apparently the result of the old head injury, was situated in the center of a small depression palpable in the parietal bone. The flap of the scalp was reflected and bleeding controlled with Raney clips. The pericranium was left intact, and there was no scarring in this plane of the scalp. Beginning at the midline, the pericranium was reflected laterally for a distance of 2 or 3 cm. This disclosed an old comminuted fracture of the parietal bone. A trephine opening was made in the caudal and mesial aspect of the operative defect through one of the old fracture lines. Nothing was seen through the thickness of the bone. About 3 mm. of the longitudinal sinus was uncovered, and the dura lateral to this showed no change. With the intention of turning down the bone flap, a second trephine was made rostrally in the same plane. When this had been carried through the bone for a distance of 3 mm., a round, irregular hole, measuring 2 or 3 mm. in diameter, presented on the lateral aspect of the trephine opening. The tip of a forceps passed through this hole encountered no resistance, and the tissue protruding through it was obviously cortical. The trephine opening was carried along cautiously; again, on its lateral aspect another large defect in the bone appeared, and, again, cortical tissue presented. Examination of a frozen section showed normal brain tissue. It seemed evident, then, that a bone flap could not be turned down without destroying a large part of this apparent herniation of cortical tissue. The trephine openings were therefore filled with bone dust, and the scalp flap was resutured with fine silk sutures through galea and scalp.

Postoperative Course.—On the afternoon following operation there developed right hemiparesis, more pronounced in the lower extremity, with increased reflexes and a positive Babinski sign on the right side. There was no aphasia. The patient complained of numbness of her right arm and leg, but careful neurologic examination showed no sensory loss. An electroencephalogram made on Feb. 29, 1944, revealed potentials of moderately decreased amplitude over the entire left hemisphere, but a second examination, on March 11, showed no difference in amplitude.

On April 12 pneumoencephalograms (figure, *B* and *C*) demonstrated slight dilatation and upward displacement of the posterior half of the body of the left ventricle. The deviation of the ventricle pointed toward the defect in the skull. It was the opinion of the roentgenographic section that this was indirect evidence of cortical atrophy in the left parietal area of the brain.

Because of abdominal pain and the discovery of the pelvic masses already noted, an exploratory pelvic laparotomy was performed on July 8, 1944, with the removal of bilateral endometrial cysts of the ovaries. Convalescence was uneventful.

The patient is now to be discharged from the service. Her only complaint is mild headache in the left frontal and parietal region and some weakness of the muscles of the right thigh and lower leg. Examination reveals only slight weakness in function of the quadriceps muscle and in dorsiflexion of the right foot.



A, lateral roentgenogram of the skull, showing erosion of the inner table due to traumatic herniation of cortical tissue. *B,* posteroanterior encephalogram, showing dilatation of the ipsilateral lateral ventricle, with the deviation point toward the area of cortical atrophy. The original trephine opening is indistinctly visualized. *C,* lateral encephalogram, with "tenting" of the posterior half of the body of the lateral ventricle. The deviation points toward the area of cortical atrophy.

SUMMARY

The degenerative process in the cranium following fracture of the skull during adolescence in this case was unusual in the destruction of the inner table, the herniation of the brain into the defect and the absence of dura mater over the area of involvement. It is hoped that a description of the findings in this case may aid in the rather difficult differential diagnosis in similar cases in the future.

MYELITIS COMPLICATING MEASLES

LAURENCE A. SENSEMAN, M.D.
SAYLESVILLE, R. I.

Myelitis as a complication of measles is rare. Only 4 cases have been reported in the American literature.[1] Ford [2] reviewed the world literature in 1928 and listed 29 cases of myelitis complicating measles. Rydeen and Glaser [1] found the reports of 8 cases since 1928, most of which are in the European literature. Little is known about the etiology and pathogenesis. Many observers believe that the condition is an acute inflammatory process caused by the neurotropic virus of measles. Finley [3] stated the opinion that allergy plays an important part in the pathogenesis. He based this belief on the fact that the complication appears at the height of the virus-antibody reaction and suggested that the myelitis is the result of a hypersensitive response on the part of the nervous system. Rivers and Schwenkter,[4] working with monkeys, produced a demyelination encephalomyelitis by the repeated intravascular injection of a suspension of rabbit brain. They stated that the character of the lesions observed was such as to suggest that they were caused by an infectious agent. Putnam [5] stated the opinion that the disease is noninfectious and that the fundamental abnormality is a spontaneous thrombosis of the small blood vessels within the central nervous system; he suggested that the abnormality may be basically allergic; i. e., an instability of the blood-clotting mechanism may be one aspect of allergy. Morris and Robbins [6] stated that measles per se is a relatively "simple" disease but that its neurologic complications require further study and interpretation. Because of the rarity with which cases of postmeasles myelitis are reported in the literature, the following case is briefly described.

REPORT OF A CASE

A. M., aged 24, a Naval Air Corps officer, was confined to the house with measles while on leave, on April 10, 1944. On the fourth day following the appearance of the rash the patient attempted to get out of bed and noticed pain and weakness in his legs. The following day he could not walk and complained of backache and headache. He noted that the skin of his legs was very sensitive and that he had a stiff neck. By noon of the same day he was unable to void. At the time of his illness he was in the home of his brother-in-law, a physician, who made a diagnosis of measles and arranged for a neurologic consultation.

Examination revealed a well developed and well nourished man who seemed rather ill. Some rash was still present. The temperature was 100 F.; the pulse rate was 80, and respiration was normal. The patient was perspiring freely. He complained of pains in the lower extremities, bachache and headache. The pupils were equal and reacted normally to light and in accommodation, and the fundi were normal. The cranial nerves were not involved. There was some nuchal rigidity. The deep reflexes were all of 4 plus intensity, and the abdominal and cremasteric reflexes were absent. Ankle and knee clonus were present and were more active on the left side than on the right. The Babinski and Hoffmann signs were not elicited. The Romberg test was not attempted because of the patient's condition.

A rather irregular area of hyperesthesis extended from the lower border of the ribs to the level of the umbilicus. Below that level sensation was definitely impaired. Urinary retention was evidenced by distention of the bladder, apparent on percussion. Lumbar puncture was productive of clear spinal fluid, with an initial pressure of 180 mm. Examination of the fluid revealed 3 white cells per cubic millimeter, a normal protein content, and 56 mg. of sugar and 725 mg. of chloride per hundred cubic centimeters. Culture of the fluid yielded no pathogens. The Wassermann reaction was negative.

The patient was transferred at once to a Naval hospital, where laboratory and physical examination gave essentially the same results as those already noted and the diagnosis of postmeasles myelitis was confirmed. Their neurologic study, made on April 14, was reported as follows: "Examination revealed normal cranial nerves; minimal weakness of the legs; absence of abdominal reflexes; an apparent increase in the deep re-

1. Rydeen, J. O., and Glaser, J.: Ascending Myelitis Complicating Measles, J. Pediat. **21**:374, 1942.

2. Ford, F. R.: The Nervous Complications of Measles, with a Summary of the Literature and Publication of Twelve Additional Case Reports, Bull. Johns Hopkins Hosp. **43**:140, 1928.

3. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

4. Rivers, R., and Schwenkter, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

5. Putnam, T. J.: Newer Conceptions of Postinfectious and Related Forms of Encephalitis, Bull. New York Acad. Med. **17**:337, 1941.

6. Morris, M. H., and Robbins, A.: Acute Infectious Myelitis Following Rubella, J. Pediat. **23**:365, 1943.

flexes, and an indefinite band of dysesthesia for superficial sensation from the fourth to the sixth thoracic dermatome on the right side and the twelfth thoracic dermatome on the left."

A progress note, on April 20, indicated that the patient was "improving rapidly and had been able to walk with assistance for the past two days." By May 1 he had "no complaints and had been ambulatory for several days." On May 6, twenty-six days after onset, he was "discharged to active duty."

Reexamination, on May 10, 1944, gave the following results: "There was no involvement of the cranial nerves; sensation was entirely normal, but the reflexes were still increased bilaterally, particularly on the left side." The patient stated that while he had slight pain in th back, he was still able to carry out his usual routin duties in the Navy. Since then, and up to Dec. 2 1944, the patient has been on full active duty. He ha lost no time because of illness.

SUMMARY

Because of the rarity with which postmeasles myelitis is reported in the literature, a case is briefly described, in which no specific therapy was instituted and the patient recovered, without residuals.

160 Chapel Street.

Case Reports

DISPLACEMENT OF THE PINEAL GLAND WITH EXTRADURAL HEMORRHAGE

M. J. Madonick, M.D., and Ignaz W. Oljenick, M.D., New York

Although displacement of the pineal gland in cases of intracranial hemorrhage [1] and subdural hematoma [2] has been described, mention of such an occurrence with extradural hemorrhage is uncommon in the literature.

We report the following case of shift of the pineal gland with epidural bleeding due to traumatic rupture of the middle meningeal artery.

REPORT OF A CASE

E. M., a Negro aged 40, was admitted to the Morrisania City Hospital in a comatose state at 5:10 a. m. on Dec. 1, 1944. He had been found unconscious in a subway station. No further information was obtainable.

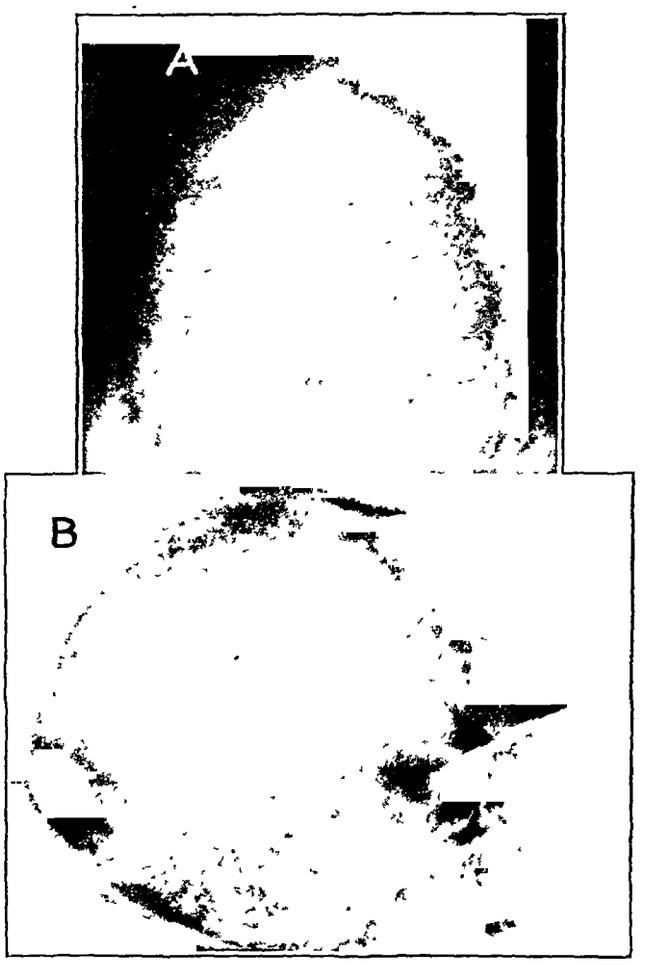
Examination on his admission to the ward revealed that he was well developed and well nourished. The pulse rate was 44 per minute, the temperature 95 F., the respiratory rate 12 per minute and the blood pressure 100 systolic and 65 mm. diastolic. There was a bruise over the left temporal region. His breath had an alcoholic odor. He was unconscious but moved his limbs on heavy supraorbital pressure. The left pupil was much larger than the right and was fixed to light; the right pupil reacted to light. The deep reflexes were hyperactive on the right side, and there were a positive Hoffmann sign and an inconstant Babinski sign on that side. Spinal tap disclosed grossly bloody fluid, which did not clear. A cell count showed 40,000 crenated erythrocytes per cubic millimeter.

At 10 a.m., five hours after his admission, the patient was still comatose but moved his limbs on stimulation of the nasal mucosa. The left pupil was fully dilated, and the right had dilated to nearly the same size as the left; neither pupil reacted to light. There was no papilledema. Meningeal signs were not elicited. There was slight eversion of the left lower limb, with a Babinski sign on the same side. The deep reflexes were depressed throughout.

The blood sugar was 118 mg. and the urea nitrogen 16.5 mg. per hundred cubic centimeters, and the Kahn reaction of the blood was negative. Urinalysis revealed nothing abnormal.

Roentgenographic study of the skull showed a linear fracture line in the left temporal region which entered the base of the skull and crossed the groove of the middle meningeal artery (figure, *B*). The pineal gland was displaced 1 cm. to the right of the midline, 1 cm. posteriorly and 0.5 cm. downward (figure, *B*), as observed by the method of Vastine and Kinney.[1a]

Operation was performed with infiltration of a solution of procaine hydrochloride containing epinephrine



Roentgenograms showing (*A*) lateral and (*B*) downward and posterior displacement of the pineal gland. A fracture line is seen crossing the groove of the middle meningeal artery.

hydrochloride. An exploratory burr hole was made over the site of the fracture line. Dark blood was seen as soon as the opening was completed. An osteoplastic flap was turned down. A large clot, estimated to contain about 500 cc. of blood, was evacuated, and the ruptured middle meningeal artery was clipped. The brain did not show any tendency to return to its normal place. On the patient's return to the ward his condition was unchanged.

The patient did not recover consciousness. The respiratory rate rose to 40 per minute and the temperature to 104 F., and bronchopneumonia developed. He died three days after operation. Autopsy, by the medical examiner, revealed a fracture, as noted in the roent-

From the Neurologic Service of Dr. N. Savitsky, Morrisania City Hospital.

1. (*a*) Vastine, J. H., and Kinney, K. K.: The Pineal Shadow as an Aid in the Localization of Brain Tumors, Am. J. Roentgenol. **17**:320, 1927. (*b*) Naffziger, H. C.: Method for the Localization of Brain Tumors, Surg., Gynec. & Obst. **40**:481, 1925.

2. Dyke, C. G., and Davidoff, L. M.: Chronic Subdural Hematoma: A Roentgenographic and Pneumencephalographic Study, Bull. Neurol. Inst. New York **7**:112, 1938. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 637. Lauder, G. H.; Browder, E. J., and Watson, R. A.: Subdural Hematoma, Ann. Surg. **113**:170, 1941. Gross, S. W., and Ehrlich, W.: Diagnosis and Treatment of Head Injuries, New York, Paul B. Hoeber, Inc., 1940, p. 55.

genogram, and a small quantity of extradural blood. Examination did not reveal subdural effusion, brain tumor or edema of the left hemisphere.

The literature dealing with roentgenologic findings in the skull in cases of extradural hemorrhage is chiefly concerned with the presence or absence of a fracture line crossing the groove of the middle meningeal vessels. Although in occasional cases such a fracture is not present,[3] the majority of authors have stated the opinion that it always exists.[4] In fact, Eynon [4c] favors trephination in all cases in which such a fracture is shown even though there are no symptoms. Mehrtens and Newell [5] described the case of a man aged 52 with a shift of the pineal gland of 0.5 cm., which returned to its position in the midline about eight weeks after an acute head injury. Their diagnosis was cerebral contusion. Schüller,[6] in a discussion of acute head injuries, stated:

> The diagnosis of an extensive hemorrhage inside the cranial cavity can be made if a displacement of the pineal shadow is present.

However, he did not describe the type of hemorrhage or its location. The only reported case that we find in which there was a shift of the pineal body with extradural bleeding was the first case reported by Falconer and Schiller,[3a] that of a man aged 30 with slight displacement of the gland. The patient recovered after operation. In Grant's [7] case a lateral view of the skull showed a slight shift of the pineal gland posteriorly, but, unfortunately, the pineal shadow was not seen in the anteroposterior view.

CONCLUSION

Displacement of a calcified pineal gland in a case of extradural hemorrhage was demonstrable in a roentgenogram. We have been able to find only 1 similar instance in the literature. We believe that a large effusion of blood must be present to produce the shift. In cases of acute head injury attention should be directed not only to the presence of a fracture line but to displacement of the pineal gland. The case described demonstrates that such a shift can be caused by extradural hemorrhage, and not by subdural or intracerebral bleeding only.

1882 Grand Concourse.

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3. (*a*) Falconer, M. A., and Schiller, F.: Middle Meningeal Haemorrhage After Head Injury Without Fracture of the Skull, Lancet **1**:532, 1942. (*b*) McKenzie, K. G.: Extradural Haemorrhage, Brit. J. Surg. **26**:346, 1938. (*c*) Turner, J. W. A.: Observations on the Cerebrospinal Fluid in Closed Head Injuries, Brit. M. J. **2**:569, 1941. (*d*) Jacobson, W. H. A.: On Middle Meningeal Haemorrhage, Guy's Hosp. Rep. **43**:147, 1886. (*e*) Woodhall, J. W.; Devine, J. W., Jr., and Hart, D.: Fractures and Other Trauma—Homolateral Dilatation of the Pupil, Homolateral Paresis and Bilateral Muscular Rigidity in the Diagnosis of Extradural Hemorrhage, Surg., Gynec. & Obst. **72**:391, 1941. (*f*) Amyot, R.: Hémorragie extradurale par rupture traumatique de la méningée, Union méd. du Canada **69**:485, 1940.

4. (*a*) Peet, M. M., in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1940, p. 133. (*b*) Munro, D., and Maltby, G. L.: Extradural Hemorrhage: A Study of Forty-Four Cases, Ann. Surg. **113**:192, 1941. (*c*) Eynon, C. M.: A Case of Symptomless Middle Meningeal Haemorrhage, Canad. M. A. J. **16**:957, 1926.

5. Mehrtens, H. G., and Newell, R. R.: Displacement of the Pineal Gland in Head Injury, J. Neurol. & Psychopath. **6**:198, 1925.

6. Schüller, A.: X-Ray Examination in Recent Head Injuries, M. J. Australia **1**:641, 1941.

7. Grant, W. T.: Chronic Extradural Hematoma: Report of a Case of Hematoma in Anterior Cranial Fossa, Bull. Los Angeles Neurol. Soc. **9**:156, 1944.

Obituaries

LLOYD HIRAM ZIEGLER, M.D.
1892-1945

Dr. Ziegler, medical director of the Milwaukee Sanitarium, Wauwatosa, Wis., died there, in the midst of his work, the evening of Jan. 8, 1945. Death came in a coronary heart attack, shortly after supper, as he was about to interview a patient. There had been no previous attack. Dr. Ziegler was a man of great energy and drive; he pursued his hobbies with as much intensity as he did his professional work. As a result, relaxation did not come easily to him; action was his life, and in action he died, at the age of 52.

(Photograph by Blackstone Studios, 20 West Fifty-Seventh Street, New York.)

LLOYD HIRAM ZIEGLER, M.D.
1892-1945

He was born in Bippus, Ind., June 1, 1892. His education and training were broad. He received his Bachelor of Arts and his Master of Arts in psychology from Indiana University in 1914 and 1916, and his Doctor of Medicine from the University of Minnesota in 1921. His internship was served at St. Elizabeths Hospital, Washington, D. C., after which he entered the United States Public Health Service, working with the veterans of the First World War, before the Veterans Administration became a separate organization. He then became house officer at the Phipps Psychiatric Clinic under Adolf Meyer, whose thoughts and comments remained deeply etched in his memory. There followed a fellowship in neurology at the Mayo Clinic and a year as resident at the Colorado Psychopathic Hospital, in Denver.

Dr. Ziegler then returned to the Mayo Clinic in 1926 as a member of the staff of the section on neurology and remained there until 1930, when he took charge of the department of neurology and psychiatry at Albany Medical College and the Albany Hospital. At Albany he plunged into a strenuous program of teaching, administration and clinical work, the last including not only his activities in connection with the school and hospital but an active private consulting practice.

In 1937 Dr. Rock Sleyster, director of the Milwaukee Sanitarium, asked Dr. Ziegler to come to Wauwatosa as his associate director. He did so, and on Dr. Sleyster's death, in March 1942, he succeeded him as medical director.

Dr. Ziegler's professional life was one of unremitting labor. This is partly attested to by the long series of his publications in neurology and psychiatry. At the time of his death he was at work on a book which was to deal with his basic ideas on the problem of human behavior and its deviations, for which he had collected a great deal of historical and technical material. Several chapters had already been written.

In his teaching, which took much of his energy and enthusiasm, he left a deep impression. It was his constant aim to stimulate, encourage and guide, without domineering, and many students and house officers remember his efforts in their behalf.

One of his distinctions, a necessarily rare one, was that of being a founding member of the American Board of Psychiatry and Neurology. He continued to serve on that board, without interruption, until he died. Only a person who has seen something of the tasks and problems of that board—even from the sidelines—can appreciate the amount of mental and physical stress involved in such an assignment.

Dr. Ziegler was profoundly aware of his duties as a citizen and was alert to the problems of government and social organization. One of these problems, with which he had had early experience, was that of the returning veteran. And one of his last activities in this field was his initiative in the establishment of a voluntary neuropsychiatric rehabilitation clinic in Milwaukee, under the auspices of the Neuro-Psychiatric Association there. Ironically, he was never able to attend that clinic. His duties on the American Board kept him away the night it opened; he had planned to come the evening he died, but a clinical responsibility intervened then also. He was active in the cause of mental hygiene and made many addresses furthering public interest in it.

No account of Dr. Ziegler's work would be complete without a mention of his closest collaborator, his wife. She shared the work in every paper he wrote, editing and transcribing, and to her he confided his notes and his ideas about the book he was writing. A closer working partnership cannot be imagined than existed between these two. He is survived by her and by his brother, Major Newell Ziegler, also a physician, and a sister, Mrs. Leland Rogers.

Dr. Ziegler was a member of many professional societies and committees, and of Phi Beta Kappa, Sigma Xi and Alpha Omega Alpha. He was less interested in the political aspects of his societies than in their medical, scientific and humanitarian activities, and he was always eager to further these objectives.

Above all, and more important than his outstanding gifts of intellect, energy and kindness, was the fact of his uncompromising integrity, a quality without which all other endowments, in a physician especially, are worse than worthless. In Dr. Ziegler's passing members of the medical profession and the public have lost a true physician and a true man, one who has left his mark not only in his written words but in the memories of those who knew him.

JOSEF A. KINDWALL, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

EMBRYONIC GRAFTS IN REGENERATING TISSUE: II THE BEHAVIOR OF THE TRANSPLANTS DURING HOST METAMORPHOSIS IN RANA PIPIENS. HENRY S. EMERSON, J. Exper. Zool. **95**:61 (Feb.) 1944.

Grafts of the embryonic eye and adjacent tissues (Rana pipiens) differentiate well in the larval tail blastema and continue to live long after the tail is fully regenerated. The eye, with lens; brain parts, and striated muscle may live over ninety days, and cartilage over one hundred days, after operation, an observation which indicates indefinite existence in this environment.

Some of the transplants disintegrate after the first week or two of differentiation. The frequency of this necrosis does not depend on the length of time in the host. Often all the graft is resorbed except the cartilage.

During the first half of the period of resorption of the host tail the transplants are not affected, but during the last half of this period most of them are resorbed. This is due to difficulties in successful transfer of the graft from the tadpole tail to the body of the young frog. After metamorphoris the transplant tissue may remain in the posterior end of the host, or, more rarely, a large graft is retained near the tip of the urostyle of the young adult frog.

Large transplants present after metamorphosis are still covered by host epidermis, originally skin of the tadpole tail. Apparently, the graft must prevent the skin of the larval tail from being resorbed. However, this epidermis approaches in coloration, degree of cornification and character of the cutaneous glands the skin of the adult body.

REID, Boston.

METHODS OF INITIATING LIMB REGENERATION IN ADULT ANURA. S. MERYL ROSE, J. Exper. Zool. **95**:140 (March) 1944.

After limb amputation, the limb stumps of adult frogs (Rana clamitans, Rana palustris and Rana pipiens) healed rapidly, with a covering of old skin. There was no regeneration except that of cartilage and skin and the formation of scar tissue. When amputation surfaces remained open because of treatment with strong salt solutions or because the skin was cut away or for some other reason, regeneration began. Regeneration of a normal distal forearm and wrist region was obtained in sodium chloride–treated frogs when the amputation was made through the midforearm. The regenerants were all abnormal in the hand region.

The author discusses at length the manner in which skin may inhibit regeneration. The treatments that evoke latent regenerative ability are drastic and may act by causing removal or dedifferentiation of inhibiting skin or by producing internal trauma, with consequent hyperemia, edema and dedifferentiation. The barrier blocking better regeneration of the frog limb appears to be early development of the dermis and fibrous scar tissue.

REID, Boston.

FURTHER EXPERIMENTAL EVIDENCE AGAINST "NEUROTROPISM" IN NERVE REGENERATION. PAUL WEISS and A. CECIL TAYLOR, J. Exper. Zool. **95**:233 (March) 1944.

No deflection of nerve fibers toward degenerating nerve has been observed in tissue culture, either in blood plasma or in liquid medium.

Sciatic nerves in the rat were allowed to regenerate in forked arteries (bifurcation of the abdominal aorta into the two common iliac arteries). The outgrowing fibers were confronted with alternative routes, either into blind channels or into channels containing degenerated nerve, tendon or fat tissue. Nerve fibers grew into blind channels with the same density and orientation as into channels containing degenerated nerve. Supposedly, "neurotropic" agents in one channel did not deflect nerve fibers in that direction. There was no tendency for nerve fibers approaching the entrance of a channel containing degenerated nerve to converge on it.

Nerve fibers in a blind channel formed irregular terminal plaques. Although there was no functional connection with appropriate end organs, these plaques persisted, without signs of resorption, for at least twenty weeks. In a single case fibers connected with a functional periphery grew to a larger size (diameter) than did unconnected fibers.

REID, Boston.

NEURAL DIFFERENTIATION OF ECTODERM THROUGH EXPOSURE TO SALINE SOLUTION. JOHANNES HOLTFRETER, J. Exper. Zool. **95**:307 (April) 1944.

The hypothesis of Barth that isolated ectoderm of an early amphibian gastrula when curled up in a favorable direction will form neural tissue was tested by corresponding explantations performed on the different areas of gastrulas of Triturus torosus and Amblystoma punctatum.

Pure ectoderm of T. torosus, cultured in saline solution, did not develop neural tissue. Irrespective of the initial curling, presumptive medullary plate and presumptive epidermis formed merely epidermis. These results confirm the generally accepted view.

Isolated ectoderm of A. punctatum differentiated into neural tissue in 60 per cent of the gastrulas. However, there was no indication that the early gastrula ectoderm is endowed with a gradient for neural formation or that the initial curling is causally related to the trend of differentiation.

Explants from gastrulas in more advanced stages showed a higher percentage of cases of neural formation when taken from the presumptive medullary plate (100 per cent) and a lower percentage when taken from the presumptive epidermis (15 per cent). Determinative stimuli must be received by the ectoderm from invaginated tissues before the time of isolation.

In explants of A. punctatum prolonged exposure to saline solution produces peripheral disintegration of the uncoated ectoderm cells. The quantity and location of neural tissue within an explant can be correlated with the proportional amount and the site of decomposition. The inductive effect of the medium may result from

stimuli from the decaying free cells or from a less severe denaturation of the surviving cells themselves.

Whenever the amount of induced neural tissue reached a certain volume, it became organized into a brainlike structure. Eyes, nasal placodes and, in rare cases, derivatives of the neural crest could be formed by any area of the gastrula ectoderm. The axial polarity of these formations was influenced by their topographic relation to the source of induction.

REID, Boston.

RESTITUTION OF THE MEDULLA FOLLOWING UNILATERAL EXCISION IN THE EMBRYO. S. R. DETWILER, J. Exper. Zool. **96**:129 (July) 1944.

Unilateral excision of the medulla in embryos of Amblystoma punctatum with closed neural folds (stages 21 to 23) may be followed by gradual restitution from the contralateral, intact, wall. This restitution is accomplished by extensive proliferation and migration of extraependymal cells of the intact side, and not from the cephalic and caudal stumps on the side of excision. The ependyma does not play any compensatory role in the proliferative processes.

In embryos with bilaterally symmetric medullas, the regenerated wall appears complete and normal except for the absence of Mauthner's cell and the failure of the vestibular system to develop. On the intact side the medial longitudinal fasciculus is slightly reduced in size.

When physiologic failures occurred, such as inability to lurch and snap at food, the medullas were observed to show disorderly and bizarre arrangements of cells and fiber bundles. In embryos with complete regeneration, the physiologic activities were essentially complete except for the limitations imposed by the absence of Mauthner's neuron and the vestibular apparatus.

In embryos with completely closed neural tubes, one-half the medulla is essentially totipotent for the whole.

REID, Boston.

SELECTIVITY OF NERVE FIBERS FROM THE DORSAL AND VENTRAL ROOTS IN THE DEVELOPMENT OF THE FROG LIMB. A. CECIL TAYLOR, J. Exper. Zool. **96**:159 (July) 1944.

The relation of nerve fibers from the dorsal and ventral roots to their terminal tissues in the developing limb bud of the frog (Rana pipiens) was investigated by means of experiments in which the spinal ganglia or portions of the spinal cord were removed at an early larval stage. In the absence of ventral root fibers, no muscular nerves were established, while a typical pattern of cutaneous nerves was produced by the remaining dorsal root fibers. When dorsal root fibers were absent, typical muscular nerves were developed, and, in addition, many small cutaneous nerves were present. Taylor suggests that the fine fibers of the cutaneous nerves may be of sympathetic origin.

A selective action of the nerve fibers results in the termination of nerves in homologous tissue. The selectivity of pioneer fibers is probably one of preneural pathways, rather than of the terminal tissues themselves. Later fibers exhibit selectivity in relation to established neural pathways.

REID, Boston.

CELL NUMBER AND CELL SIZE IN THE ECTODERM DURING NEURULATION (AMBLYSTOMA MACULATUM). ROY GILLETTE, J. Exper. Zool. **96**:201 (Aug.) 1944.

An estimation was made of changes in ectodermal volume, cell number and cell size during neurulation in Amblystoma maculatum. This was done by measuring the cross section areas and by counting nuclei in fixed sections selected at equal intervals along the entire length of 10 neurulas, representing various stages.

An increase of 23 per cent in the number of cells present in the total ectoderm without an increase in total volume of the ectoderm during neurulation indicates that the mitotic activity represents cleavage. An analysis of various regions shows that the decline in cell size is a general feature of all parts of the ectoderm. No significant difference in cell size was observed between the dorsal regions, containing mostly neural tissue, and the lateral and ventral regions, containing epidermal cells.

There is a pronounced gradient in cell size in the anterior-posterior axis of the neurula, with the smaller cells anteriorly. This gradient is present throughout neurulation and is regarded as a manifestation of the animal-vegetal gradient which originated during cleavage stages.

Gillette concludes that localized cell enlargement and differences in mitotic rate are not involved in neurulation up to the meeting of the neural folds. The thickening of the neural plate is attributed to a concentration in the dorsal region of cells from both the lateral and the dorsal areas. The thickening of the neural plate, though to a certain extent autonomous, is part of the general pattern of morphogenetic movements of the entire neurula.

The author suggests that the folding of the plate is a direct result of the contraction process, which progresses at a greater rate at the surface than in the deeper tissues. Thus, the surface coat of Holtfreter may be an important factor in neurulation, as well as in gastrulation.

The interpretation of epithelial expansion and contraction in terms of "surface tendencies" of the cells provides a method for the quantitative analysis of morphogenetic movements occurring in epithelial layers.

REID, Boston.

THE EFFECTS OF PERIPHERAL FACTORS ON THE PROLIFERATION AND DIFFERENTIATION IN THE SPINAL CORD OF CHICK EMBRYOS. VIKTOR HAMBURGER and EUGENE L. KEEFE, J. Exper. Zool. **96**:223 (Aug.) 1944.

Hamburger and Keefe made an analysis of the hypoplasia of the lateral motor columns at the brachial level caused by extirpation of the wing bud in early chick embryos, and of the hyperplasia observed in similar segments of the cord when a supernumerary wing was implanted beside the host wing.

In embryos with unilateral extirpation of the limb there was a slight effect of the operation on the rate of proliferation, as shown by mitotic figure counts made during the peak of activity at the brachial level of the spinal cord. This effect appeared to be transient. Separate cell counts made of the lateral motor and of the nonmotor ventral neurons of the brachial and lumbosacral levels of the cord showed that the total cell numbers were strikingly identical for the two sides in all instances, whether of limb extirpation (4 embryos) or of wing transplantation (1 embryo). The deficit of motor neurons in cases of hypoplasia was balanced by an excess of nonmotor neurons. In the case of motor hyperplasia the surplus was compensated for by a deficit in nonmotor cells. It is concluded that peripheral factors control the differentiation of potential neuroblasts into motor neurons. The mechanism of peripheral control is discussed, and an inductive effect of differentiated

primary motor neurons on adacent indifferent cells is postulated.

In view of these results and of other recent studies, the authors suggest that a similar effect of peripheral factors on differentiation of motor neurons exists also in the urodeles.

REID, Boston.

Physiology and Biochemistry

A STUDY OF GNOSIS, PRAXIS AND LANGUAGE FOLLOWING SECTION OF THE CORPUS CALLOSUM AND ANTERIOR COMMISSURE. ANDREW J. AKELAITIS, J. Neurosurg. **1**:94 (March) 1944.

The purpose of this study was to evaluate the role of the anterior commissure in interhemispheral connections after partial or complete section of the corpus callosum. The tests used toward this end included observations on body laterality, a study of the higher visual functions in each homonymous field, praxis, auditory gnosia, tactile gnosia, temporal-spatial gnosia and language functions.

The first patient had had drainage of an abscess of the frontal lobe and was left with residual generalized grand mal and petit mal seizures and episodic aphasia. Three years later the corpus callosum was sectioned completely, with resulting continuation of the convulsions and no major impairment of the higher functions. One year later the anterior commissure was cut, with the same results.

In the second patient, a depressed woman, the genu and the anterior half of the body of the corpus callosum, the anterior commissure and the right limb of the fornix were sectioned; this was followed by bilateral leukotomy. The higher functions studied in her case likewise were not impaired.

The authors concluded that there exist interhemispheral neuronal pathways other than those present in the corpus callosum and the anterior commissure.

WHITELEY, Philadelphia.

THE PHYSIOLOGICAL BASIS OF CONCUSSION. A. EARL WALKER, JERRY J. KOLLROS and THEODORE J. CASE, J. Neurosurg. **1**:103 (March) 1944.

With the use of general anesthesia, concussion was produced in a large number of cats, dogs and monkeys by the impact of a weight falling against the fixed skull. Tetanic spasm, respiratory and circulatory changes, alterations in reflexes and electrical disturbances were used as criteria of the concussive state. Cerebral concussion gave rise to the following clinical manifestations: (1) tetanic phenomena, consisting of immediate generalized muscular spasm, due to intense stimulation of the central nervous system; (2) respiratory changes, manifested by sudden spasm of the intercostal and diaphragmatic muscles, which produces a gasp, followed by normal or irregular respiration or by apnea; (3) changes in blood pressure, causing arterial hypertension, due to stimulation of the vasomotor centers, with production of peripheral vasoconstriction; (4) bradycardia, due to excitation of the vagus fibers, and (5) reflex changes, shown by the abolition of tendon reflexes and heightening of the threshold of the anterior horn cells.

The electroencephalogram revealed a generalized initial discharge, followed by a pronounced increase in the frequency of cortical activity, with subsequent relative inactivity and a gradual return to normal. The intense electrical discharge was conveyed to all parts of the nervous system.

The authors conclude that the physiologic basis of concussion is the traumatic breaking down of the polarized cell body membranes of the neurons of the central nervous system, with resulting firing of the axons, producing widespread excitation, both centrally and peripherally. The important factor in depolarization is the rapid oscillations in intracranial pressure. Furthermore, the altered permeability of the cell wall following breakdown of the membrane is the basis of postconcussion cerebral edema.

WHITELEY, Philadelphia.

PROBLEMS OF FATIGUE AS ILLUSTRATED BY EXPERIENCES IN THE DECOMPRESSION CHAMBER. JOHN ROMANO, GEORGE L. ENGEL, E. B. FERRIS JR., HENRY W. RYDER, JOSEPH P. WEBB and M. A. BLANKENHORN, War Med. **6**:102 (Aug.) 1944.

Forty-three adults were exposed repeatedly to simulated altitudes of 35,000 feet (10,250 meters) in a decompression chamber. They were studied clinically, psychologically and by various laboratory tests. In most cases each exposure was terminated because some incapacitating symptom of decompression sickness developed, but if none occurred the exposure was terminated at the end of three hours.

Three types of fatigue were observed: 1. Muscular fatigue occurred in all subjects, was unrelated to decompression sickness and disappeared with training. 2. Fatigue related to boredom occurred most often during exposures with no decompression sickness, when the subject remained inactive at the induced altitude for long periods. 3. The third type of fatigue was not related to muscular effort or to boredom. It was experienced by 24 of the 43 subjects and sometimes was related to decompression sickness and sometimes not. It was delayed in onset and resembled fatigue experienced during or after anxiety situations. The results of laboratory tests, including the electroencephalogram, the blood count and circulatory reactions to changes in posture, showed no direct correlation with any type of fatigue. In a few instances damage to tissues subsequent to decompression sickness undoubtedly contributed to the fatigue.

PEARSON, Philadelphia.

TONIC AND CLONIC RESPONSES OF THE CEREBRAL CORTEX FOLLOWING HYPERVENTILATION. EFREN C. DEL POZO, Arch. de neurol. y psiquiat. de Mexico **7**:35 (March-April) 1944.

The experiments recorded by del Pozo were performed on cats anesthetized with dial, the electrodes being applied directly to the cortex, which was covered only by the leptomeninges. The stimuli came from an induction coil at intervals of two or three minutes to avoid facilitation and extinction. Hyperventilation was produced by artificial respiration, with a cannula in the trachea. Blood pressure readings were taken by placing a cannula in the left carotid artery. The responses of the cortex to faradic stimulation were recorded electroencephalographically. In all cases hyperventilation caused diminution to disappearance of the usual cortical responses to faradic stimulation. In addition to shortening the duration of response, there was diminution of frequency and voltage of the electric potentials. The decrease in blood pressure during hyperventilation is not the cause of this diminution of cortical response. The author conducted experiments in which the fall

in blood pressure was avoided. The possibility of cortical inhibition due to an increase in afferent stimulation of the lungs and other viscera was ruled out by sectioning the vagus nerves and by performing experiments on animals with transverse sections through the midbrain. The same diminution of response during hyperventilation was observed. When artificial respiration was employed with air containing 4 per cent carbon dioxide, the cortical responses did not diminish or disappear. If the concentration of carbon dioxide was 8 to 10 per cent, the cortical responses persisted, even though no attempt was made to prevent lowering of blood pressure. The author offers no explanation of the mechanism for depression of cortical activity following faradic stimulation of the brain with hyperventilation. These results seem to contradict those of Brody and Dusser de Barenne, who reported an increase in responses to electrical stimulation of the cortex during hyperventilation.

SAVITSKY, New York.

PHYSIOLOGICAL INTERPRETATION OF THE CONVULSANT ACTION OF METRAZOL. CARLOS GUTIERREZ-NORIEGA, Rev. de neuro-psiquiat. **7**:14 (March) 1944.

Gutierrez-Noriega studied the action of metrazol administered in convulsant doses in decerebrate dogs. The experiments were performed on six groups of animals, transverse sections being made at various levels of the brain stem. Eight to 10 animals were used for each level, the sections being made (1) between the medulla and the pons, (2) at the midpons, (3) between the pons and the mesencephalon, (4) between the upper and the lower quadrigeminal tubercles, (5) above the mesencephalon and (6) above the hypothalamus. Metrazol was injected sixty to ninety minutes after operation; the dose (convulsant for normal dogs) was 20 mg. per kilogram for the first injection and 30 to 40 mg. per kilogram for the second injection, an hour later. The results of this experiment confirmed the observations of other investigators that the intensity and frequency of the convulsions diminish in direct proportion as the brain stem is cut at successively lower levels. It was further observed that tonic convulsions originated chiefly in the brain stem, specially in the medulla, pons and mesencephalon, while clonic convulsions had their origin in the upper nuclei (the mesencephalon, the hypothalamus and possibly the cortex).

Analysis of these results, together with the effects obtained by local injection and use of the Horsley-Clarke apparatus and bioelectric recordings, leads to the conclusion that the nerve discharges produced with stimulating drugs originate simultaneously or in rapid succession in many nerve centers. Summation, both temporal and spatial, takes place in the neurons of the spinal cord and the medulla and secondarily in other parts of the neuraxis, and the epileptic seizure follows. It is likely that the quantity of metrazol reaching each cell is subliminal for most of the neurons and that a liminal dose would be lethal. In all probability, the prolongation of the convulsion is due not to the continued action of the drug on the neurons but to the internuncial circuits of reexcitation.

The author calls attention to two theories regarding the pathogenesis of epileptic convulsions. According to one of them, the disturbance resides in the isolated neuron, the discharge rhythm of which is intensified or prolonged beyond the normal. The second theory admits no difference between the reaction of the normal neuron and that of the isolated neuron during a convulsion; the pathologic phenomenon resides in the entire neuron system and is due to the widespread summation and synchronization. The author's experiments tend to sustain the second theory, although the two are not in opposition.

PIETRI, New York.

SCHIZOPHRENIA AND PARANOID PSYCHOSES AMONG COLLEGE STUDENTS. THEOPHILE RAPHAEL and LEONARD E. HIMLER, Am. J. Psychiat. **100**:443 (Jan.) 1944.

Raphael and Himler studied the incidence and features of schizophrenic and paranoid psychoses in the student body at the University of Michigan. They found the incidence of schizophrenia to be 1 in 655 of the student population and that of paranoid disturbances to be 1 in 3,070. Schizophrenia was more common among male students and paranoid psychoses among female students. Forty-two per cent of the patients with schizophrenia were first seen in the acute phase of the illness. Students with paranoid psychoses were in the main considerably older than those with schizophrenia. Forty-four per cent of the patients were referred during their first semester. Evaluations of the personality at the time of admission to college showed a high incidence of unsatisfactory and doubtful ratings. Aided by regular contacts with the mental hygiene unit 46.1 per cent of the schizophrenic students and 60 per cent of the students with paranoid disorders were able to pursue their studies. The authors stress the importance of a proper screening of prospective students.

FORSTER, Philadelphia.

NEUROTIC REACTIONS IN PARACHUTISTS. JOSEPH G. KEPECS, Psychoanalyt. Quart. **13**:273, 1944.

All, or nearly all, parachutists fear jumping. This produces a conflict between the desire to escape and the demands of duty and personal pride. When a neurotic reaction develops, its occurrence and character depend on the sum of two factors: the man's life experiences, which, through the agency of repressed fears and unconscious fantasies, may invest a situation with terror far beyond the actualities, and the events of the traumatic situation, i. e., actual physical injury or narrow escapes.

Kepecs reports 5 cases of neuroses in parachutists and concludes that the neurotic symptoms express (1) attempts to repeat the traumatic situation, (2) efforts to escape the danger, (3) attempts to heal the wounds inflicted on the personality by the trauma, (4) attempts to repeat the trauma in terms of analogous threats to infantile existence which have been regressively reactivated and (5) other neurotic conflicts which parasitize on the available symptoms. The reactivation of infantile problems and the considerable degree to which the actual conflict is expressed in terms of childhood fears are attributable to three factors, which also shed light on the inability to give up the neurotic defenses after the way out of the danger has been successfully achieved:

1. A struggle against the social periphery of the superego, which is perceived also as a struggle against parental demands. This conflict has two phases: first, the attempt to escape the danger, and, second, the attempt to avoid recognizing the significance of the escape which the ego conceives as a defeat and which produces reproaches of cowardice from the superego. On a more immature level, this constitutes an escape

from dangerous activity by becoming passive, and it unconsciously signifies coming to terms with the father and escaping death by sacrificing the genital. The regressive expression serves as a defense against the recognition of the desire to escape.

2. The threat of destruction or dissolution of the personality overwhelms the ego and results in a contraction and diminution of the ego's powers. As a result the subject's adaptations take on an infantile character.

3. The direct threat to life and to the integrity of the body is connected symbolically and by association with specific early experiences, which may be regarded as sensitizing. Oral desires and oral ways of dealing with the world are important. Strong preexisting oral fixations appear to predispose to reactions of this type.

PEARSON, Philadelphia.

REMARKS ON THE COMMON PHOBIAS. OTTO FENICHEL, Psychoanalyt. Quart. **13**:313, 1944.

The simple phobic pattern is as follows: In a situation which unconsciously represents an instinctual temptation, anxiety is felt instead of excitement, and subsequently the situation, and therewith the anxiety, is avoided. The phobic situation does not always represent a sexual temptation, but may represent an aggressive impulse, an early frustration or an unconsciously feared punishment. If the anxiety is a warning signal against temptation, why does it become so severe? Anxiety functions as a danger signal to avoid the development of a traumatic situation when the organism is so flooded with emotion that the normal mechanisms for mastering excitation are inadequate. The function of anxiety fails in phobic anxiety. The ego, which gives the signal of danger, starts something which it cannot contest because the organism, through a series of previous repressions, has dammed up forces which are waiting the opportunity for discharge.

The temptation or punishment is displaced to the phobic situation as a ruse to escape greater dangers. In some cases an external object is substituted for another. In other cases there is an external projection of an inner danger, or a feeling of guilt is replaced by external fears.

All patients with phobias show regression the gains of which are secondary. Certain paths of displacement are determined directly by the specific nature of the warded-off instincts. For instance, a fear of being devoured serves the purpose of a defense against oral demands, of being on the street, against exhibitionism, and the like.

Agoraphobia wards off exhibitionism, scoptophilia and muscle pleasure in walking. There is a close connection between the sensory apparatus which registers anxiety and that which registers sensations of equilibrium and position in space. Conflicts emanating from the sexualization of infantile sensations of equilibrium give rise to equilibrial phobias. The sexualization occurs in some persons because sensation of equilibrium and of bodily movement in space has become the sole representation of infantile sexuality. In falling asleep and in anesthesia there occur equilibrial and spatial sensations. The association between these sensations and sleep leads to a phobia of death, and a high percentage of death phobias are phobias of sensation of equilibrium and of space. Fears of falling asleep and of being narcotized are expressions of underlying fears of being overwhelmed by psychologically painful sensations of disequilibrium in space.

Claustrophobia demonstrates the basic role of the projection of internal sensations. The patient dreads his own emotional excitement and attempts to escape from it by leaving the space in which he finds himself when the excitement occurs. The patient fears that his ego control will break down if he becomes enormously excited. The development of the clinical picture of claustrophobia is facilitated by two physiologic circumstances. First, the imposition of any hindrance to bodily movements, either real or fantasied, itself causes anxiety, through the damming of drives. Second, any state of anxiety is accompanied physiologically by a feeling of being closed in, so that an external closeness, or the idea of it, facilitates the mobilization of the entire anxiety syndrome.

The first physiologic syndrome of fear is a feeling of constriction in the chest, accompanied by difficulty in breathing. It is in an attempt to protect himself against unpleasant sensations that the patient with agoraphobia feels the street, and not his own body, as constricted or not constricted.

In some patients the underlying mechanism is that of projection. The danger instinct is projected, for example, onto the street, and then the patient is able to avoid the anxiety by avoiding the street. In other patients this does not happen, but the danger instinct constantly reemerges from repression and has to be projected again and again. This depends on the economic equilibrium between instinct and anxiety which results from the personal experience.

The person who requires stimulation or distraction to enable him to work well is really suffering from disturbances of concentration produced by an inner restlessness, which is relieved in surroundings which provide external restlessness, just as certain people may enjoy thunderstorms because, the noise being outside rather than inside themselves, they do not need to feel afraid of their own inner confusion and anxiety. There are innumerable prejudices and anxieties associated with types of landscapes, changes of weather and season, light and darkness, times of the day, and the like, which are narcissistic projections of inner feelings, for consciousness of nature is less a process of becoming aware of its physical elements than one of becoming aware of feelings evoked by the contemplation of these elements, or of the inner ideas which these elements symbolize.

The fear of overwhelming inner excitement is an important source of anxiety in the phobias. The fear of castration and the fear of being abandoned in childhood are the root of the fear that the ego will be flooded with unmanageable quantities of excitement because the child is not able to satisfy its demands. When the ego has developed sufficiently to achieve adequate instinctual satisfaction and to master reality, instinctual temptations should not be avoided as dangerous but should be anticipated as pleasurable. In the adult ego the idea that excitement is dangerous emerges only when satisfaction is frustrated by endogenous obstacles, i. e., by fear of castration or of loss of love, originating in an animistic misinterpretation of the external world.

PEARSON, Philadelphia.

STUDIES IN VITAMIN B DEFICIENCY WITH SPECIAL REFERENCE TO MENTAL AND ORAL MANIFESTATONS. A. GREY CLARKE and F. PRESCOTT, Brit. M. J. **2**:503 (Oct. 23) 1943.

Clarke and Prescott report the results of a study of 17 patients with deficiency of members of the vitamin B complex, which represented 2 per cent of all patients seen by them in an outpatient department. The nervous

disorders of all but 1 patient were classified as functional. The occurrence of oral lesions due to nicotinic acid deficiency associated with symptoms usually considered as psychoneurotic was a constant finding. All but 2 patients responded to therapy with members of the vitamin B complex. Three patients had relapses after periods of from two to five months without treatment but responded to further treatment. The study revealed a parallelism between the manifestations of a deficiency of the vitamin B complex and those of psychoneurosis.

ECHOLS, New Orleans.

PROGRESSIVE CEREBRAL ISCHAEMIA. TREVOR H. HOWELL, Brit. M. J. **2**:746 (Dec. 11) 1943.

Howell made a study of 27 senile patients, among whom were two groups whose mental deterioration seemed to be associated with cerebral ischemia. The first change noted was a vague or muddled state of mind in a patient previously lucid. This was followed by a stage of restlessness, often increasing to violence. As the restlessness wore off, the pulse became perceptibly weaker, and the patient drifted into a terminal coma. A progressive fall in blood pressure was noted in all cases in which readings were taken. Howell believes that the relation between a falling blood pressure and the appearance of cerebral symptoms in arteriosclerotic subjects suggests that progressive cerebral ischemia is the basic pathologic condition.

ECHOLS, New Orleans.

NERVOUS BREAKDOWN IN THE NAVY: DOMESTIC DIFFICULTIES AS A CAUSAL FACTOR. GEOFFREY TOOTH, Brit. M. J. **1**:358 (March 11) 1944.

Of the environmental factors which cause nervous breakdowns in the Navy, the two which are not directly connected with hazards of war are (1) the conditions and the type of service and (2) domestic difficulties. Tooth studied the effects of these factors on patients in two hospitals in different parts of the world. It was noted that 35.6 per cent of the men with nervous breakdowns due to domestic difficulties were invalided, whereas 26.6 per cent had breakdowns leading to invalidism because of enemy action or conditions of service. It was further observed that when there are multiple etiologic factors of which one is domestic trouble, the virulence of the reaction was twice as great as when domestic worries alone were responsible. Analysis of the types of domestic difficulties revealed that the most frequent cause of breakdown was real or suspected infidelity of the wife or fiancée, with illness or death of a near relative a close second. The author emphasizes the need for thorough investigation of cases and suggests that a psychiatric social worker be appointed to Naval depots in an effort to reduce the incidence of nervous breakdowns leading to invaliding as a result of domestic worries.

ECHOLS, New Orleans.

ANXIETY; ALOPECIA AREATA; NEUROFIBROMATOSIS; AURICULAR FIBRILLATION. DOUGLAS HUBBLE and C. H. ROGERSON, Brit. M. J. **1**:486 (April 8) 1944.

Hubble and Rogerson report an unusual case of a patient exhibiting three disorders of unknown cause and pathogenesis: alopecia areata, neurofibromatosis and auricular fibrillation, each of which developed at the peak of a period of great frustration and anxiety. The patient, an intelligent, impulsive, resentful person, possessed exceptional drive and ambition, with an obsessional desire for success. The authors postulate that in this case the auricular fibrillation and the alopecia areata were related to the neurofibromatosis. Quinidine therapy resulted in resumption of normal cardiac rhythm. The case represents the varied factors (genetic, constitutional, psychologic, environmental and mechanistic) which must be taken into consideration when one is evaluating disease in man.

ECHOLS, New Orleans.

THE RELATION OF DERMATOLOGY TO PSYCHIATRY. F. F. HELLIER, Brit. M. J. **1**:583 (April 29) 1944.

Hellier discusses the significance of the psychologic approach in the study of dermatologic conditions, for "embryologically speaking at least, psychiatry is an offspring of dermatology, and a fundamental association persists into adult life." Of the two groups of cutaneous conditions (cutaneous diseases proper and cutaneous reactions) the latter is primarily concerned with the makeup of the patient. Consequently, treatment should be based on the discovery of the immediate factor which caused the present attack and the adjustment of the patient's attitude to life and his dermatologic condition. The latter may be difficult to accomplish, but it is most important if permanent benefit is to be obtained. Among the cutaneous reaction diseases discussed are eczema, rosacea, alopecia areata, lichen planus and hyperhidrosis.

ECHOLS, New Orleans.

CARDIAC NEUROSIS [NEUROCIRCULATORY ASTHENIA] AS A MANIFESTATION OF HYPOGLYCEMIA. R. GREENE, Lancet **2**:307 (Sept. 2) 1944.

Greene describes 5 cases in which the clinical symptoms were interpreted as those of DaCosta's syndrome (effort syndrome), or neurocirculatory asthenia. In all cases there were precordial pain, giddiness or faintness and perspiration on exertion of mild to moderate degree. In some cases headache, palpitation or tachycardia was present as well. In each case there was laboratory evidence of hypoglycemia when the attacks were reproduced. All attacks were aborted by administration of sugar. Each patient had a normal heart.

Since neurocirculatory asthenia is brought on by fear, which, in turn, causes liberation of epinephrine, and since the early symptoms of hypoglycemia are those of epinephrine activity, it is not surprising that the two conditions may be confused. Indeed, they "are identical." Since the symptoms of hypoglycemia may be relieved by adequate diet, "an effort should be made to evaluate the part played by abnormal carbohydrate metabolism in producing the symptoms of each patient with DaCosta's syndrome or a similar cardiac neurosis."

MCCARTER, Boston.

Meninges and Blood Vessels

GLYCOSURIA IN MENINGITIS. FRANK FERGUSON and DAVID BARR, Ann. Int. Med. **21**:173 (Aug.) 1944.

Ferguson and Barr report their observations on 72 consecutive patients with meningitis. Spontaneous glycosuria occurred in 16 of the patients and in over one third of the 26 patients who had meningococcic meningitis. Glycosuria was encountered in cases of meningitis caused by the meningococcus, pneumococcus, staphylococcus and tubercle bacillus. In 1 patient the organism was not isolated. Ketosis, hyperglycemia and diminished dextrose tolerance frequently accompanied

the glycosuria. The glycosuria was transient, and it persisted beyond the third day in only 3 of the 16 patients. Coma with glycosuria and ketosis at the onset of meningitis may lead to a faulty diagnosis of diabetic ketosis. Delay in the establishment of a correct diagnosis of meningitis and subsequent proper management may have serious consequences.

GUTTMAN, Philadelphia.

MENINGOCOCCIC MENINGITIS: SULFADIAZINE THERAPY. EMIL H. GRIECO and ARTHUR M. COVE, Ann. Int. Med. **21**:194 (Aug.) 1944.

Grieco and Cove report clinical and laboratory observations on 20 consecutive patients with meningococcic meningitis. As soon as the diagnosis was established, an initial dose of 5 Gm. of sodium sulfadiazine was administered intravenously, even when the patient could take the drug orally. Subsequent doses of 2 Gm. were given regularly every four hours, either orally or intravenously, as determined by the patient's ability to receive medication. One gram of sodium sulfadiazine was administered every four hours until the temperature returned to normal, and from this point, four times a day daily for the next seven days. As long as the urinary output was 750 cc. or more during the first twenty-four hours fluids were not administered parenterally. This method of sulfadiazine therapy afforded adequate concentrations of the drug in the blood, effected satisfactory clinical response and resulted in few complications, none of which left permanent residua.

The Waterhouse-Friderichsen syndrome was encountered in 2 patients, 1 of whom recovered after the parenteral administration of an aqueous extract of adrenal cortex.

GUTTMAN, Philadelphia.

MENINGOCOCCEMIA WITHOUT MENINGITIS: A STUDY MADE AT THE STATION HOSPITAL, FORT GEORGE G. MEADE, MARYLAND. HAROLD W. POTTER, ROGER D. REID and LEWIS H. BRONSTEIN, Ann. Int. Med. **21**: 200 (Aug.) 1944.

Potter, Reid and Bronstein report clinical observations on 11 patients who had meningococcemia without evidence of meningitis. The outstanding and most useful sign was the cutaneous eruption. Only 1 of the 11 patients failed to exhibit this sign. Joint and muscle pains, present in 6 of the 11 patients, formed another outstanding characteristic of the syndrome. Headaches were present in 10 of the 11 patients.

The authors conclude that "the diagnosis can be strongly suspected before the report of the blood culture in a patient with the skin eruption and headache if the possibility of this disease is kept in mind. Sulfadiazine resulted in rapid cure without sequelae in all our cases."

GUTTMAN, Philadelphia.

FULMINATING MENINGOCOCCIC INFECTION (WATERHOUSE-FRIDERICHSEN SYNDROME). P. A. HERBUT and W. E. MANGES, Arch. Path. **36**:413 (Oct.) 1943.

Herbut and Manges review the history of the Waterhouse-Friderichsen syndrome and report 4 cases, which bring the total number to 125. Because of the rapid onset and the high fever, often associated with leukocytosis and a fulminating course with fatal termination, the syndrome has long been regarded as an overwhelming septicemia. Although the meningococcus has been shown to be the causative agent in over 60 per cent, the authors believe that this figure is much too low. It is the consensus that adrenal apoplexy is responsible for the death of the patients. The authors, however, concur with Aegerter that there is no proof that death from the Waterhouse-Friderichsen syndrome is due to adrenal failure rather than to toxicity caused by invasion of the blood stream. In 3 of their cases there were bilateral and massive adrenal hemorrhages. In the fourth case only a single small, circumscribed hemorrhage was noted in the right adrenal gland, while the medulla of both glands showed areas of hypoplasia. Sections of skin in 3 cases showed, respectively, congestion of the dermal capillaries; congestion, hemorrhages and inflammation, and congestion, hemorrhages, inflammation and thrombosis. In 3 cases with predominantly septicemic symptoms there were dissociation of the hepatic cords, cloudy swelling of liver cells, sinusoidal congestion, perisinusoidal edema and diffuse infiltration with polymorphonuclear leukocytes. Meningococci were isolated post mortem in pure culture from the spinal fluid and the blood from the heart in 1 case and ante mortem from the spinal fluid and material from the nasopharynx in 1 case. Cultures of the blood taken post mortem in the remaining 2 cases yielded respectively a member of the Friedländer group and Staphylococcus aureus. Sections of the skin in each of these cases and of the adrenal gland in the former cases disclosed within the capillaries gram-negative, bean-shaped diplococci, morphologically similar to meningococci. It is probable, therefore, that in most, if not all, of the cases of the Waterhouse-Friderichsen syndrome in which other organisms have been isolated the disease was caused by meningococci.

J. A. M. A.

MENINGITIS DUE TO PITTMAN AND NON-PITTMAN STRAINS OF H. INFLUENZAE. J. GORDON, H. E. DE C. WOODCOCK and K. ZINNEMANN, Brit. M. J. **1**:779 (June 10) 1944.

Gordon, Woodcock and Zinnemann report 2 cases of meningitis due to the non-Pittman type of Haemophilus influenzae in which treatment with sulfapyridine was successful. The strains of H. influenzae isolated in these cases did not differ from the strains regularly isolated in cases of bronchiectasis. Because so few cases of meningitis due to H. influenzae typed serologically have been reported, the authors describe 3 cases in which the strains isolated were of Pittman type B; in 2 of these 3 cases in which the course was fulminant and fatal, little or no treatment was given. In the third case response to sulfapyridine treatment was good, but more of the drug was required than in the 2 cases of meningitis produced by the non-Pittman type. Because so little is known of the relative response of non-type-specific and type-specific strains of H. influenzae to the sulfonamide compounds, the authors believe that in cases of meningitis of this origin, the organism should be typed, in an effort to determine any possible differences in prognosis.

ECHOLS, New Orleans.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

PAUL I. YAKOVLEV, M.D., *Presiding*

Regular Meeting, March 16, 1944

Psychiatric Problems in Conservative Treatment of Ulcerative Colitis. DR. ERICH LINDEMANN.

For 45 patients with ulcerative colitis, verified by proctoscopic examination, the psychosocial history, the personality makeup and the response to therapeutic interviews were studied. The history showed various forms of bereavement as the most important precipitating factor. For 26 of the 45 patients a close time relation existed between the loss of an important person and the onset of the illness. Ten other patients had ceased to interact with an important person because of disillusionment or rejection. A surgical procedure preceded the onset of the illness of 4 patients. Three patients had shown notable behavior abnormalities, and the onset of the illness was preceded by signs of a beginning psychosis, which, however, did not develop further after the colitis started. The personality of the patient was marked by poverty of human relationships, an inability to make and hold friends of their own age, and by a need for considerable activity throughout the day but lack of resourcefulness in finding avenues for such activity. Rewarding patterns of social interaction seemed not to be indigenous to these patients. This state of affairs became conspicuous only when a key person on whom the patient was dependent and from whom he had borrowed patterns of interaction was removed from the "social field." This dependency, which seems to be a special form of social integration, became a threat to the patient after bereavement because he was then confronted with a poverty of successful patterns of conduct and with a tendency to primitive behavior patterns, colored by fantasies of extreme violence and social behavior marked by aggressiveness and overcritical, demanding and "spoiled-child" attitudes. This trait was often shown in the request for consultation from the medical service.

Such inclination to primitivation of behavior (regressive tendencies?) often becomes manifest only after the psychiatrist has established growing intimacy with the patient in interviews. Early attempts at exploration with the usual psychiatric technic of reconstructing the life history were invariably followed by a primitivation of the patient's fantasies and behavior. The patient would leave treatment, not to return until vigorously urged by the internist, or would develop overwhelming anxiety from fear of being overcome by primitive impulses or would report actually having experienced psychotic manifestations, such as auditory hallucinations, a sense of alien influence or somatic delusions. Other patients became conspicuous in the ward through dilapidated behavior, such as impulsive outbursts or defecating on the floor, and needed special nursing care. The behavior, stream of talk and communicativeness in explorative interviews rapidly changed to uncommunicativeness, retardation and often blocking. Objective time records of the verbal and gestural activity during interviews (interaction chronogram) demonstrated a remarkable reduction in the capacity for interaction during progressive interviews.

It became evident that the patients were as vulnerable to the establishment of new contacts as they were to the loss of social interaction.

The reactions shown by the patient were strikingly similar to behavior patterns associated with acute grief, which were studied after the Cocoanut Grove disaster.

The technic of psychologic management must avoid the traditional methods of psychoanalytic inquiry. The contact must be brief, not permitting the development of regressive tendencies, hostile feelings or affectionate attachment. The relationship must, rather, be an identifying one, in which the patient copies behavior patterns of the psychiatrist and makes use of them in the same manner as he previously did with the patterns of the person whom he has lost. If this difficult problem is solved, the patient usually goes through a period of imitating the psychiatrist in his relations with other patients in the ward, and of idealizing the psychiatrist, attributing to him an inordinate status in the hospital and testing out his availability and willingness to serve the patient as a source of new patterns of conduct. After such a relationship is established, it is often possible to review the bereavement with the proper emotions of depression and sorrow. The patient may go through a period of "nervousness" and worry, which might, superficially, appear detrimental to visceral functions but which is a prerequisite for readjustment.

While the personality, the precipitating crisis and the habitual reaction patterns of the patients seemed uniform, ulcerative colitis did not develop in the large majority unless another, somatic, factor brought about a special predisposition in the colon. Gastrointestinal disturbances in the family, acute gastrointestinal infections, measles with gastrointestinal involvement and surgical procedures seemed to be nosogenic. Psychologic determination in terms of traumatic experiences in childhood was rare; in only 2 patients did I find a confirmed history of severe difficulties in bowel training. In no patient did mucous colitis precede the ulcerative colitis.

DISCUSSION

DR. STANLEY COBB: I should like to emphasize first the fact that the psychiatrist is working with the physician, and working on equal terms. It used to be a matter of handing the patient over completely, not working on an equal footing. Patients used to be handed back and forth, again and again. Here, at last, the internist and the psychiatrist have worked out a method of working together.

Second, Dr. Lindemann has introduced something new in psychiatric therapy. It has been taught for years that the method of chief reliance was exploration through interviews. This exploration was efficacious in many cases. In cases of ulcerative colitis it is harmful.

Last, Dr. Lindemann is to be congratulated on working with an anthropologist. With Dr. Chapple's invention of actually measuring certain interpersonal reactions, one does not have to rely on impressions after an interview. All this leads in the right direction. Psychiatric interviews can eventually be made something worthy of the name of science.

DR. CHESTER M. JONES: The significant feature of Dr. Lindemann's presentation is the clear demonstration of the importance played by emotional disturbances in a chronic organic disease involving the digestive tract, such as chronic ulcerative colitis. In this disease, psychiatric considerations comprise only one of several significant factors; but because the underlying cause of the disease is still not known, it is of extreme importance that each of the various factors be controlled as completely as possible.

There can be no doubt that adequate psychiatric measures are helpful in controlling the activity of ulcerative colitis in numerous instances. At times psychotherapy may constitute a real hazard to the patient's health because of resulting emotional disturbances, transient though they may be. For this reason it is important that the psychiatrist and the internist collaborate closely, shifting responsibility as the need arises, so that the patient as a whole may be adequately observed and controlled as nearly as possible.

The importance of overstimulation of the autonomic nervous system secondary to emotional disturbances cannot be overemphasized and probably represents a fundamental conception of gastrointestinal physiology which involves not only this disease but many other conditions, such as ulcer and diverticulitis. Symptoms referable to the digestive tract probably represent nothing more or less than an exaggeration of the normal physiologic processes involving motility, local or general blood supply, tonus and secretion. All these factors may be conditioned by disturbances involving the autonomic nervous system. These changes have been clearly demonstrated by Wolff in his work on the stomach and by White and Jones in their observations on the sigmoid portion of the colon.

DR. H. HALE POWERS, Wellesley, Mass.: While Dr. Lindemann was speaking, I was reminded of a case that occurred in my experience almost thirty years ago. The young woman had previously been treated for ulcers of the colon in one or two hospitals; then she recovered under treatment with bromides and only a little psychotherapy. I do not know how long she remained well.

I have been wondering how patients with ulcerative colitis differ in personality from patients with gastric ulcer. Patients with gastric ulcer whom I have known have been as socially inclined as the average. As Dr. Lindemann has said, it is perhaps well for physicians to react, to a limited extent, against psychoanalysis. The goal is to keep patients as normal as possible, and the normal person has a certain content in his mind that he does not disclose to any one. Psychologic exploration should not be carried out unnecessarily, any more than surgical exploration. Surgical exploration can produce adhesions. One knows many patients who are adherent to certain psychiatrists. In those patients psychologic adhesions have been produced.

DR. FRANK C. D'ELSEAUX: Dr. Lindemann and Dr. Jones have demonstrated that an internist and a psychiatrist can, and in cases of ulcerative colitis must, work in close association with each other. Dr. Jones has pointed out that in many cases the disease starts with an intestinal infection which may be common to a number of people, in only 1 of whom ulcerative colitis will develop, and that the large bowel shows circulatory changes under emotional strain. I wonder whether it may be said that the patient who subsequently has ulcerative colitis uses his bowel in a different way psychophysiologically throughout life and that his bowel is, therefore, more vulnerable to infection, and subsequently to ulceration.

Dr. Lindemann stressed the important function of "role psychiatry." While such a method has been used by many psychiatrists, it is doubtful that any have used it so wholeheartedly as has Dr. Lindemann, with such careful attention to detail or with such full realization that unless it is carried out in such a manner it may do more harm than good, harm which may be fatal to the patient with ulcerative colitis.

I wish that Dr. Lindemann, who obviously has much greater knowledge of the psychologic mechanisms involved than he indicated in his paper, had not limited himself to pointing out a mere temporal relation between occurrence of a qualitatively specific incident and the appearance of a symptom in a patient with certain personality attributes. I wish he had given more dynamic insight into why this type of personality develops, why the patient has come to have this special dependence and restriction of objects on which he is dependent, and why when there are so many leave-takings, he reacts more strongly than others to separation. One wonders what is the special meaning of a separation to such a person. One also wonders why the bowel is the origin of election and why ulcerative, instead of mucous, colitis develops.

Finally, I should like to ask Dr. Lindemann how he feels about the use of a more deeply investigative type of therapy during a period of remission, or whether this must be modified even then.

DR. J. MARTIN WOODALL: Many of the patients with colitis seem to do extremely well symptomatically with a nonexploratory type of therapy. I can speak particularly of patients with mucous colitis, with whom I have had an extensive experience. Psychiatrists who deal with the psychoneuroses in an organized hospital setting, where an opportunity is afforded for detailed observation, have frequently noted the extraordinary influence on the patient's symptoms of his reaction to other persons—to the physician, to a nurse or to another patient. This is particularly noticeable with symptoms of a psychosomatic nature. Such an interpersonal relationship can be a potent factor in the control of symptoms seriously interfering with normal physiologic processes. The delineation of the components of such a relationship gives invaluable information as to the dynamic basis of the patient's illness and furnishes important clues to the methods to be employed in appropriate general management. If subsequent exploratory therapy is indicated, this interpersonal reaction becomes the foundation for its organization. Dr. Lindemann is to be congratulated on so lucid and comprehensive a presentation of an extremely informative paper.

DR. G. COLKET CANER: I should like to ask Dr. Lindemann whether any particular type of emotion brought on exacerbations of this condition.

DR. PAUL I. YAKOVLEV: I wish to ask Dr. Lindemann to what extent these emotional situations to which the patient is responsive are of his own making. Are the situations a projection of the personality of the patient, or are they a part of his own background?

DR. ERICH LINDEMANN: I wish to thank the discussers, especially Dr. Jones, who has been helpful in giving a proper balance to the discussion. What I said would have been one sided if he had not emphasized the internist's point of view. In this work I found it extremely interesting to treat a condition in which a severe structural disorder had to be approached by psychiatric methods. New skills had to be developed. These methods are related to what Whitehorn used to call supportive therapy of the psychoses. They are similar

to methods used with children, especially young children, and allow a limited expression of primitive behavior. These ideas are not as new as they seem.

In answer to Dr. Powers and Dr. D'Elseaux, I must have given the false impression that I was proposing to give up exploration altogether. This is not true. Exploration is impossible only for the emergency state of ulcerative colitis; similarly, I should not recommend it for schizophrenia. Certainly, after the emergency period which I stressed is over, the patient enters another phase of the illness, in which one learns a good deal by exploration about the patient's former development and about his present defective social relationships. In the latter the patient will recapitulate his childhood habits of behavior. One of the most fascinating problems which arise is this: In what way has it come about that such a person has not learned to acquire more lasting relationships? Why has he not acquired lasting patterns of effective behavior? Why can some of them behave effectively only when a certain key person is present? Sometimes the answer is to be found in the patient's early background. For instance, a boy whose father's patterns of behavior are objectionable to him may copy his mother as a model and become a "sissy." His subsequent social isolation comes from wrong steps in the early acquisition of patterns of social interaction. Evaluation of the early influences in the patient's life is important, but one must not mobilize dangerously powerful emotions connected with some early experience. A good deal of information may be gained, however, not from exploration but from observation of the patient's interaction with other patients. For instance, the young girl whose case I discussed had a delayed grief reaction to the death of her mother following an abortion, which occurred when she was 3 years old; this reaction was acted out in the ward but was not recalled as a memory. Two weeks after I started psychiatric work with her, she had a panic attack in the middle of the night. The house officer was called. The patient showed him a bit of stool which she believed to be an embryo. Identifying herself with her mother, she wondered whether she was aborting and whether she must die too. The next week she refused to eat, being afraid of finding drugs in her food such as her mother used to induce an abortion. A week later she was in a severe depression, with feelings of self depreciation. She was blaming herself for seeming to try to separate her father and stepmother. In all this, exploration in verbal terms was replaced with observation. The situation is much like that encountered in child psychiatry; I use observation of behavior, much as is done in the play technic.

Dr. Woodall, I agree that patients with psychosomatic disturbances as a group are so dangerously ill that supportive treatment is important. With respect to the organ of choice, patients with ulcerative colitis and patients with peptic ulcer present quite different problems. There is much similarity between patients with rheumatoid arthritis and patients with ulcerative colitis. Ten per cent of patients with ulcerative colitis have rheumatoid arthritis.

In reply to Dr. Caner's question, I am cautious in using the term emotion because it is so vague. The essential emotion in cases of ulcerative colitis is sorrow. My work with patients with this disease was what started me working on grief reactions, and I have found that these patients present an abundantly interesting area for psychiatric study and treatment.

HARRY C. SOLOMON, M.D., *Presiding*

Regular Meeting, April 20, 1944

The April meeting of the society was held at the Boston Psychopathic Hospital for the presentation of clinical material by the members of the hospital staff. The latter reviewed briefly some of the problems which are of interest to the members of the staff or which might intrigue the members of the society or which offered some novelty.

The program consisted of rapid presentations of the effect of frontal lobotomy and a modification of the surgical technic of this procedure; a preliminary review of the effect of penicillin on neurosyphilis; a consideration of the possible damage to the mentality of patients who have received electric convulsion therapy, and the use of sodium amytal in the exploration of the psychic content of an apprehensive or inhibited patient.

Frontal Lobotomy. DR. JAMES L. POPPEN.

The experience which my associates and I have had with frontal lobotomy has been so recent that as yet we are not justified in expressing a dogmatic opinion as to the proper method of carrying out the leukotomy. It is through the efforts of Dr. H. C. Solomon that Dr. Horrax and I have been urged to attempt relief of the dreadful anxiety which some of the patients suffer.

Several methods have been advocated for carrying out an adequate leukotomy. Watts and Freeman deserve considerable credit for corroborating the work of Egas Moniz and for popularizing the procedure. Since the technic of Lyerly seems to be a more adequate surgical approach, I have adopted his plan, with a few minor modifications. Two trephine openings are made 2.5 cm. in diameter. A button of bone is removed from each side of the skull 3.5 cm. from the midline just anterior to the coronal suture line. A small dural flap is made. A ventricular needle is then inserted into the most anterior portion of the lateral ventricle. As it enters the ventricle, it is withdrawn, directed just in front of the anterior pole of the lateral ventricle and inserted until the ridge of the sphenoid wing is felt. The needle is then withdrawn, and the tract acts as an excellent guide to the direction and plane of the incision in the white matter that is to be made by the electrosurgical suction unit. A lighted retractor gives excellent exposure and visualization, allowing the surgeon to perform a complete leukotomy and, at the same time, to save all the larger branches of the cortical vessels as they are encountered medially, inferiorly and laterally. The anterior cerebral artery can be well visualized and therefore protected from injury. The falx can be seen through the arachnoid, with the larger cortical vessels left intact. It is important that the white substance just anterior to and beneath the lateral ventricle be completely divided down to the ridge of the sphenoid wing. In our first case the symptoms recurred a few days after operation. The incisions were reopened, and it was noted that the white matter between the anterior horn of the lateral ventricle and the ridge of the sphenoid wing had been incompletely sectioned. Notable improvement in the patient's condition occurred after the dissection had been completed.

No changes in the state of consciousness have been noted in the patients operated on after they aroused from the anesthesia.

The operation, though seemingly minor, should not be undertaken lightly. All the more conservative measures

should be given adequate trial for a sufficient period. Unfortunately, in this particular operation the neurosurgeon is, and should be, merely a technician. The decision as to the suitability of the patient for operation falls directly on the shoulders of the well trained psychiatrist. The operation is safe only in the hands of a competent neurosurgeon.

CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *President, in the Chair*

Regular Meeting, April 11, 1944

The Future of Neurology: Presidential Address. DR. R. P. MACKAY.

Erotomania (Lymphomania) as an Expression of Cortical Epileptiform Discharge. DR. T. C. ERICKSON, Madison, Wis.

This paper was published in full in the March 1945 issue of the ARCHIVES, page 226.

Effects of Lesions of the Periaqueductal Gray Matter in Cats and Monkeys. DR. PERCIVAL BAILEY and DR. E. W. DAVIS.

Patients with lesions around the midbrain sometimes pass into a strange state, which has been called "akinetic mutism." It was thought possible that the periaqueductal gray matter, a very old and fundamental formation in the brain stem, might be related to this condition. After some experimentation, a method was developed of destroying this nerve tissue without injury to other parts of the brain. The effect on cats was to reduce their activity almost to zero when the lesion was extensive. An aggressive, dangerous male monkey would sit apathetically in a corner of the cage. If he was given food, he would eat but would not bother to move for it if it was out of his reach. If he was irritated roughly, he would bare his teeth but make no attempt to attack. In general, the behavior of all these animals was characterized by this lack of "drive." Serial sections through the brain proved that the injury had been confined to the periaqueductal gray matter in almost all cases. Extension of the lesion into the periventricular gray matter of the diencephalon added a cataleptic component to the syndrome. The animals were not unaware of their surroundings but reacted much less actively and less continuously to their environment and lapsed quickly into indifference. (The behavior of the cats was illustrated by motion pictures, and photographs of the lesions were demonstrated.)

It is tempting to correlate these observations with dynamic psychology. These basal formations are obviously closely related to the instinctive drives and are regulated and controlled by the vast superstructure of the cerebral hemispheres. In man, however, one must remember the steady corticalization of many functions subserved in lower vertebrates, even in lower mammals, by subcortical mechanisms.

DISCUSSION

DR. R. P. MACKAY: One is reminded of Dr. H. Douglas Singer's theory that lesions of the diencephalon underlie schizophrenia. The behavior of certain of these akinetic animals does suggest catatonic stupor. Perhaps this interesting work may lead to something important in the field of this disease.

DR. VICTOR E. GONDA: May I ask for a somewhat more detailed description of the technic with which the authors could so exactly induce such a well circumscribed lesion with electric current?

DR. PERCIVAL BAILEY: The lesion was made with an electrical apparatus which delivers a constant amperage. The behavior we have described was first observed by Magendie. He produced it in unanesthetized rabbits by destruction of the heads of both caudate nuclei. Mettler obtained it with removal of the frontal lobes. I have seen Mettler's moving pictures of his animals. The ability to progress in our animals is better than in his; his animals showed leaping rather than progression. Dr. Davis and I tried to reproduce this behavior by removal of the frontal lobes, but were never able to get results as good as Dr. Mettler's. Just what the mechanism is that releases such behavior I do not know.

Book Reviews

Foster Home Care for Mental Patients. By Hester B. Crutcher, Director of Social Work, State of New York Department of Mental Hygiene. Price, $2. Pp. 199. New York: The Commonwealth Fund, 1944.

This book deals with foster home care for mentally ill patients. The author discusses the meaning and values of family care, including administration and the results achieved, the selection of patients, the selection of homes and the supervision of the patients, giving case histories to illustrate her observation. Miss Crutcher describes two methods of organizing family care: the colony and the district system. Family care of the mentally ill has existed for some time, both in this country and in some other countries, but it has not been an adequately developed or adequately staffed community procedure in the United States.

For a long time state hospitals in this country have needed relief from overcrowding. Family care is a good means of meeting this problem. Even with wartime difficulties there are in the state of New York at present as many patients under family care as would almost fill a state hospital. In this state only patients who are unable to work for their own maintenance or to look after themselves if given a relief check are classified as family care patients. The program began in 1933, with the placement of mentally defective patients. It was first financed by colony funds, which had accumulated over a period of years.

Thirty-two women patients, who had been in one institution many years, were placed in homes which were considered ideal for care of patients of this type. The women adjusted so well that the number was increased as rapidly as funds for such care were available. So successful was this placement of mentally defective patients that in 1935 legislative authorization was provided for the family care of the mentally ill. Each institution was allowed to use maintenance funds for the placement of patients under family care with the understanding that a deficit up to $10,000 in this sum would be allowed by state budgetary authorities. This placement plan of the mentally ill has been developing slowly and carefully. In general the institutions developing the program have placed patients in homes within a 30 mile (48.3 kilometer) radius of the institution. However, both Letchworth Village and Middletown State Hospital have placed patients in a rural area about 75 miles (120.6 kilometers) from both institutions. This area of the state was regarded as ideal for the extensive development of a family care program, especially for the patient requiring continuous treatment. After three years there were over 600 such patients living with families in various parts of the state. It was felt that a good foundation had been laid for the relatively rapid development of the program, when its financial support was withdrawn. Fortunately, permanent restoration of funds for continuing this work was made on July 1, 1940, so that, again, patients can enjoy the advantages of community life. The New York State Department of Mental Hygiene has been responsible for the allocation of funds and for the general direction of the program.

The rate paid by the state was originally $4 a week, but this has since been raised, and the present weekly rate ranges from $6 to $8, with an allowance of 25 cents a week to the patient for spending money. Clothing is furnished by the institution responsible for the patient if no relatives or friends can be found to furnish this. Patients who have funds of their own or whose relatives are willing and able to pay more than the state rate are placed in family care accommodations in keeping with the amount paid for the patient's care. Usually, 1 to 6 patients are placed in a home. However, in certain instances, spacious homes have been found which accommodate 10 to 15 mentally defective patients.

Seventeen of the twenty civil state hospitals and three of the five state schools have family care programs. At the beginning of the present war approximately 1,900 patients were under family care, but, owing to shortage of personnel and changes in family life, this number has gradually decreased. As of Jan. 1, 1944 approximately 1,800 patients were in family care, the ratio of patients receiving family care to patients in state hospitals being 1.5 per hundred, and the ratio of mentally defective patients receiving family care to those in state schools, 3.1 per hundred. The large state hospitals in New York city have not been able to develop family care to any great extent. One or two elderly patients are thus placed in some homes. When these patients have shown they can adjust and manage their financial affairs, they are transferred onto convalescent status with old age assistance. Patients suitable for family care are selected and transferred to hospitals in the upstate district where homes are available. In spite of the present shortage of medical and social service staff and the curtailment of transportation facilities, the service is now firmly established as a supplement to institutional care.

The book is recommended as describing and evaluating an important adjunct facility for the care and rehabilitation of the mentally ill.

Freud's Contribution to Psychiatry. By A. A. Brill, Ph.B., M.D. Price, $2.75. Pp. 245. New York: W. W. Norton & Company, Inc., 1944.

Brill was the Salmon lecturer in 1943. He chose to discuss Freud's contribution to psychiatry, and these lecturers are now available in book form. Brill is the translator of many of Freud's books and his close and faithful friend for many years.

Much of the volume is concerned with the history of the development of the psychoanalytic movement. The first three chapters concern Dr. Brill's introduction to psychoanalysis, from the descriptive psychiatry then in vogue in New York to the interpretive psychiatry in Europe. Brill's quest for knowledge concerning hypnotism led him to Paris, just as Freud had been led earlier. He then studied at Burghölzli, where, together with his chief, Bleuler, and Jung, Riklin, Abraham and Hans Meier, Freud's association technic was first used. A résumé of Freud's professional life follows this introduction. The whole development of psychoanalysis is unfolded, beginning with Freud's fascination by hypnotism, his studies of hysteria and his first attempt to describe a case psychoanalytically, namely, the famous

Dora case. By 1908 Freud's basic works had been written, and of these "The Interpretation of Dreams" was the most significant.

The remainder of the book is devoted to presentations of the most notable theories, ending with Freud's final preoccupation with man and race and the postulate that all disturbances in these spheres have their origin in the Oedipus complex. Brill stresses particularly Freud's belief that the psychoses differ from the neuroses in degree rather than in kind and that psychoneurotic illness never occurs in a person with a normal sexual life. Most of the concepts are illustrated by Brill by his own cases, which he interprets in a strictly freudian manner.

This book of 234 closely printed pages affords pleasant and informative reading. There are glimpses of the author's quiet humor, which add charm and at the same time make one sense his humility. The book constitutes an excellent summary of Freud's own vast psychoanalytic contribution, seen through the eyes of his American pioneer. Time alone will show the inherent value in all his theories. Psychoanalysis is slowly changing and growing, and a clear knowledge of its origins is essential to all who wish to interpret these changes, as well as to students of the problems of people and their relationships. The volume is highly recommended.

Insulin Shock Therapy Study. By the Temporary Commission on State Hospital Problems. Pp. 97. New York, 1944.

This study of the effectiveness of insulin shock in the treatment of schizophrenic patients is the report of the Temporary Commission on State Hospital Problems, appointed by Gov. Thomas E. Dewey of New York. The study is based on the results of insulin therapy of 1,128 patients at the Brooklyn State Hospital between January 1937 and June 1942, and the data for a control group of 876 patients admitted to five other state hospitals during the same period who did not receive any form of shock therapy but whose treatment was presumably comparable in other respects. The most dramatic finding emerging from this study is that insulin treatment effected a saving of 286,695 days of hospital care and a saving of $80,274.60 in cost of food and clothing to the state. Accepting the validity of the non-insulin-treated patients as a control group, the commission concludes that the insulin treatment itself was the significant differential factor in reducing the period of hospitalization. The natural recommendation is made that the use of insulin shock treatment be made available for all schizophrenic patients until some more effective therapy is demonstrated.

That a statistically significant difference in length of stay in the hospital was found between the insulin-treated patients and patients not so treated is incontrovertible. However, from the data included in this report, the proposition that the insulin itself is the significant therapeutic factor would seem to be warranted only as a working hypothesis, rather than as a demonstrated fact. The main criteria used for evaluating effectiveness of treatment are length of hospitalization and level and stability of adjustment after discharge. While length of hospitalization is a focus of practical interest to state finance and the taxpayer, and while a legitimate reduction in the period of hospitalization is an economic desideratum in itself, it is not a definitive criterion for evaluating the precision of the insulin technic in effecting basic qualitative changes in the personality organization of schizophrenic patients and in the underlying patterns of emotional reaction from which the psychotic symptoms are derived. In actual practice, state hospitalization is resorted to for the schizophrenic patient when the family or the community can no longer tolerate his disturbed behavior and is terminated when the behavior has again come within the limits of tolerability. While an attempt is made in this study to evaluate qualitative differences in the effective level of posthospital adjustment, and differences favoring the insulin-treated group are found, they are small. For instance, in terms of gainful employment, a difference of only 10 per cent is noted between the insulin-treated patients and the patients not so treated. Actually, too, only 14 per cent more insulin-treated patients than non-insulin-treated patients were at home at the time this study was concluded, although 21 per cent more had been discharged. The figures for readmission are also of interest, 42 per cent of the insulin-treated patients having one or more readmissions to the hospital as compared with 31 per cent of the non-insulin-treated patients.

What the data in this study demonstrate is a positive relation between insulin shock treatment and a shortened stay in the hospital. In terms of hospital economy, it would be of interest to know what percentage of the total expenditure for the care of schizophrenic patients is represented by the saving of $80,274.60, given in this report only as an absolute figure. With the goal of increased economy in mind, some questions with regard to the control group not answered by the data in this report come to mind. For instance, how frequently was the possibility for discharge for patients in this group reviewed? May not days of hospitalization beyond the patients' actual needs have accumulated out of administrative cautiousness? That is, was each discharge in the control group actually made at the earliest possible date? It would also be of interest to have comparisons of the insulin group with a control group who received a comparable investment of trained psychotherapeutic attention.

The reviewer commends the method of approach employed in this study, particularly the inclusion of a control group. This in itself raises the study to a scientific level well above many statistical evaluations of insulin shock treatment. In the main this report is both thoughtful and thought-provoking and represents a valuable contribution to the literature of insulin shock therapy.

Pain. Research Publications, Association for Research in Nervous and Mental Disease. Vol. xxiii. Price, $7.50. Pp. 468, with 116 illustrations. Baltimore: Williams & Wilkins Company, 1943.

John Hilton, from his vast clinical experience, wrote about pain in 1876, and nearly seventy years later Sir Thomas Lewis from his vast clinical experience, wrote about pain. There is probably as much new information about pain in the volume under discussion which has accumulated in the year since the publication of Lewis' book as there was in all the years preceding.

Pain is a subjective phenomenon, and consequently does not lend itself well to animal experimentation. Hence, in the great majority of the papers collected in this volume man has been the subject of the experiments. One must pay tribute to the "pains-taking" attitude of both experimenters and subjects, since many of the experiments were obviously disagreeable and could have been carried out only for the purposes of extending the boundaries of knowledge.

New methods are ingeniously applied by means of which a sharp end point is attained, useful for the quantitative study of thresholds of pain. The differentiation

between the "bright" pain, carried by the large, rapidly conducting A fibers, and the "dull" pain, carried by the C fibers, is stated in fuller detail, and with precision, on the basis of superbly controlled experiments. The threshold of pain and the severity of the reaction to pain are differentiated, the former being relatively constant while the latter is much more variable. Sensations as they relate to pain, such as cold, heat, itching and pressure, are brought into the picture. Few of the authors would admit that the last word has been said. But methods have been devised to bring further information on pain to the man who deals in pain, the physician.

The second part of the volume takes up the locale, rather than the qualitative aspects, of pain. Here the discussion is more uneven, owing partly to the nature of the organ studied and partly to the preoccupations of the authors. Headache is particularly well covered, the contribution of the extracranial structures being adequately presented for the first time. The applied physiology that has blossomed as the result of the neurosurgical procedures is a welcome addition to knowledge of the mechanisms and pathways of pain.

In contrast to some of the other recent volumes of this series from the Association for Research in Nervous and Mental Disease, this volume is eminently readable and understandable.

Patients Have Families. By Henry B. Richardson. Price, $3. Pp. xx plus 408. New York: The Commonwealth Fund, 1945.

This book is the report of the director of an important investigation recently carried on by a group of health agencies in New York city. In it the relation of the patient to his family and his family background is surveyed from several angles. It has long been recognized that methods of obtaining information on this subject and its subsequent utilization are totally inadequate in the present practice of medicine. As the author, Dr. Henry B. Richardson, points out, only the old-fashioned general practitioner was in a position to evaluate the true nature of the patient's symptoms in relation to his family and background. Only the psychiatrist is at present equipped to analyze the material and to put it to therapeutic use.

The investigation of the family background of a number of patients seen in the wards and clinic of a city hospital was made with the cooperation of physicians, psychologists, social workers and public health nurses. Many organizations took part in the project, which was carried out over a number of years. For the most part the results are reported in the book through case or family histories. In parts of the book the "family as the unit of illness" and the "family as the unit of treatment" are considered. There is then a discussion of the present and of the future, in which there may be better utilization of the family unit in hospital and medical practice through cooperation of the various medical specialty units. In the case histories one finds concrete examples of the failure of medical practice of today because of inadequate utilization of background material related to the patient.

The author is to be complimented both on the detailed demonstration of the nature of the defects and on the suggestions for future improvement. Not only are practical details elaborated, but there is a scholarly discussion of earlier psychologic and sociologic material related to the subject in which he describes the homeostasis of the family group. The bibliography is excellent and draws from a wide field.

Neurology of the Eye, Ear, Nose and Throat. By E. A. Spiegel and I. Sommer. Price, $7.50. Pp. xi plus 667, with 117 illustrations. New York: Grune & Stratton, Inc., 1944.

This book may best be termed an uneven production. Spiegel and Sommer have attempted to do in one volume what Wilbrand and Saenger carried out in six volumes for the eye, and Alexander and Marburg in four volumes for the ear. Even the bibliography is overweighted, with over 1,700 references—far too many for a work of this size. Spiegel's wide acquaintance with the physiology of the nervous system appears on nearly every page, but his meticulousness gets him in trouble with the reader because of the frequent balancing of negative and positive results in complex experiments. Furthermore, the authors cannot seem to keep physiology in the background when they come to discuss clinical applications. It is as though they thought that even if the clinical results are not definite they should be because experimental work gives clearcut results. Aside from Spiegel's own original contributions to the neurology of the eye and ear, this must be considered as a scholastic rather than a scholarly work. There is a vast amount of information contained in the book, together with suitable illustrations, but the information is imperfectly digested. Possibly the book represents an attempt to get away from the oversimplification of neurology. If so, it has succeeded admirably.

News and Comment

APPOINTMENT OF DR. LEO M. DAVIDOFF

Dr. Leo M. Davidoff has been appointed attending neurologic surgeon at Montefiore Hospital for Chronic Diseases, New York, and will commence his duties on a full time basis on or about September 1. He has also been appointed to the rank of professor of clinical neurologic surgery at Columbia University College of Physicians and Surgeons.

Dr. Davidoff will continue with his consulting practice in neurosurgical problems at his office, which will be located in Montefiore Hospital.

Dr. Davidoff served as resident in neurologic surgery under Dr. Harvey Cushing in Boston and was later affiliated with the Neurological Institute of New York. Before coming to Montefiore Hospital, he was chief of surgery and attending neurologic surgeon at the Jewish Hospital of Brooklyn.

Archives of Neurology and Psychiatry

VOLUME 53 MAY 1945 NUMBER 5

EXPERIMENTAL STUDIES ON HEADACHE

TRANSIENT THICKENING OF WALLS OF CRANIAL ARTERIES IN RELATION TO CERTAIN PHENOMENA OF MIGRAINE HEADACHE AND ACTION OF ERGOTAMINE TARTRATE ON THICKENED VESSELS

C. TORDA, M.D., AND H. G. WOLFF, M.D.

NEW YORK

Distention of cranial arteries induces pain of an aching quality.[1] On the other hand, when the distended cranial arteries associated with the attack of migraine headache are constricted, the pain is abolished.[2] The speed with which vasoconstrictor agents, such as ergotamine tartrate, reduce the intensity of the headache approximates the rate of constriction of the cranial arteries. In many patients the headache arises in the distended branches of the external carotid arteries,[3] although any or all of the cranial arteries may be involved at one time or another in migraine headache. Secondary to such pain from prolonged distention of cranial arteries, the skeletal muscles of the neck and scalp contract. Such prolonged contraction in itself becomes painful and adds a component to the migraine headache.[4]

Certain additional phenomena of the migraine headache which have not been studied before are the subject of this discussion. They may be described as follows: After several hours of migraine headache, involving for example the temporal artery, the vessel may appear more prominent and distended than normal and becomes more readily palpable through the skin. Further, instead of being readily collapsible, it becomes rigid, pipelike and less readily compressible by the palpating finger. Also, the artery may be tender when compressed. Patients so affected may report that after the first hour or two of an attack of migraine headache the quality of the headache changed in that the initial pulsating or throbbing was less conspicuous or was absent and the pain became a steady ache.

To account for these changes, we have postulated that after sustained dilatation there occurs a transient change in the structure of the wall of the temporal artery, namely, thickening or edema of the muscular and adventitial structures. To validate this conception, sections taken from the temporal artery of patients during attacks of migraine headache involving this structure were studied. Microscopic examination of such sections suggested that there was thickening of the arterial wall. However, exactly comparable control sections of the same or other arteries during periods of freedom from headache cannot be obtained.

It has been necessary, therefore, to approach the problem through animal studies by determining whether transient changes within the arterial walls, such as are relevant to this discussion, can follow prolonged vasodilatation.

To achieve this end, the use of a vasodilator agent, preferably one present in the body, was desirable. Acetylcholine was selected. It is emphasized that the selection was not based on evidence that acetylcholine causes migraine headache; the drug was chosen because it is an active vasodilator, is promptly destroyed locally and can be infused for several hours without endangering the

This study was aided by a grant from the Josiah Macy Jr. Foundation.

From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College.

1. Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Headache Produced by Histamine, Arch. Neurol. & Psychiat. **35**:1054 (May) 1936. Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. **1**:907, 1939. Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance in Headache, Arch. Surg. **41**:813 (Oct.) 1940.

2. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, A. Research Nerv. & Ment. Dis., Proc. **18**:638, 1938; Arch. Neurol. & Psychiat. **39**:737 (April) 1938. Sutherland, A. M., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of the Mechanism of Headache in Migraine, Hypertension and Fever, ibid. **44**:929 (Nov.) 1940.

3. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache: A. Contrast of Histamine Headache with the Headache of Migraine and That Associated with Hypertension; B. Contrast of Vascular Mechanisms in Preheadache and in Headache Phenomena of Migraine, Arch. Neurol. & Psychiat. **45**:199 (Feb.) 1941.

4. Simons, D. J.; Day, E.; Goodell, H., and Wolff, H. G.: Experimental Studies on Headache: Muscles of the Scalp and Neck as Sources of Pain, A. Research Nerv. & Ment. Dis., Proc. **23**:209, 1943

life of the animal. It is suggested that the thickening of arterial walls demonstrated in the following experiments may be analogous to transient thickening of arterials walls during a prolonged attack of migraine headache.

EXPERIMENTS WITH A VASODILATOR SUBSTANCE

Method.—Six cats were anesthetized with an aqueous solution of dial with ethyl carbamate and monoethylurea. One ear was removed as a control for histologic study. Mammalian Ringer's solution [5] containing 0.5 mg. of acetylcholine bromide per hundred cubic centimeters was infused into the common carotid artery on the side of the intact ear by inserting a hypodermic needle into a branch with the tip of the needle reaching the common carotid artery and pointing in the direction of the blood stream. The rate of inflow (ascertained by a drop recorder in the inflow circuit) was so adjusted that the total input of the acetylcholine solution during the two hours of infusion was 10 cc.

The blood pressure was registered by means of a cannula inserted into the femoral artery and leading to a mercury manometer. Acetylcholine in the concentrations used induced no significant changes in the blood pressure, the heart rate or the rate of respiration.

After two hours of infusion the remaining ear was removed. The ears were fixed in Bouin's solution, and cross sections were prepared for histologic study. Five strips of tissue were cut from each ear, the corresponding strips being equidistant from the tip. The strips were approximately 2 mm. wide, and the sites from which they were taken were separated from each other by about 2 mm. The strips were, therefore, representative samples of the ear from tip to base. Each strip was divided into two to four pieces for convenience in cutting and mounting. From one to three sections for histologic study were made from each piece, making twelve to twenty sections from each ear. The sections were prepared with the trichrome stain.[6] The width of the walls of all arteries containing visible smooth muscle was measured. An area of the cross section of the wall, including intima, stratum muscularis and adventitia, of each of the arteries was projected onto paper by means of a camera lucida, using a magnification of 15 by 40, and a tracing made. This area was then measured with a planimeter. From 100 to 250 cross sections of arteries from each ear were thus measured.

Frozen sections were also prepared. These sections showed changes similar to those noted in ears fixed with Bouin's solution; but since the frozen sections were technically less satisfactory for measuring, the results have not been included in the data presented.

Results.—On gross inspection the infused ears were noted to be slightly thicker than the control ears; and when they were compressed between the fingers, pitting was observed. The infused ears were redder, and the blood vessels appeared larger. Irregularly scattered about were small, reddened regions, presumably the result of diapedesis.

Microscopic examination showed that the walls of the arteries of the infused ears were sometimes thickened. Here and there the intima was slightly swollen, and the nuclei of the smooth muscle cells were farther apart than normal. There was no cellular exudate or hyperplasia. It seemed, then, not only that the arteries were dilated but that their walls were thicker.

Cross Sectional Areas of the Walls of Arteries of Ears Infused with a Vasodilator Substance (Acetylcholine) and of Control Ears *

	Cross Section Area of Wall				
	0.5 to 0.75 Sq. Cm.		5 to 7. 5 Sq. Cm.		0.5 to 7.5 Sq. Cm.
Procedure	Number of Arteries, %	Total Area of the Cross Sections Within the Group, Sq. Cm.	Number of Arteries, %	Total Area of the Cross Sections Within the Group, Sq. Cm.	Total Area of Cross Sections of the Walls per 100 Arteries, Sq. Cm.
Control	21.9	12.80	3.6	19.40	185.50
Ear infused with acetylcholine	12.0	7.50	18.3	109.00	268.00

* The values given are the values for the projected (camera lucida) sections and not actual dimensions of arteries.

Measurements of the projected areas of cross sections of the arterial walls are summarized in the table. These quantitative data are expressions of the magnifications of the camera lucida and the microscope and do not represent actual dimensions of the arteries. The arteries were classified according to magnitude of the projected areas of the cross sections into eleven groups. The magnified thickness of the walls varied from 5 to 48 mm. Sections from the control series had a larger number of arteries with the smallest cross section area of the wall, whereas the infused ears had a larger number of arteries with the greatest cross section area of the wall. As a result of infusion the cross section area of the walls of the arteries was increased throughout the whole range of artery sizes, as evidenced by the shift of greatest frequency from the arteries of smaller area toward the arteries of greater area. Also, the total area of the walls of the arteries obtained from the ears infused with acetylcholine was much

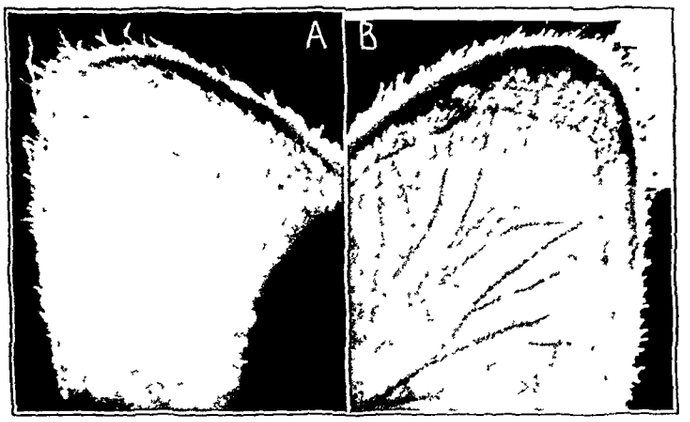
5. Mammalian Ringer's solution contains 0.900 Gm. of sodium chloride, 0.030 Gm. of potassium chloride, 0.025 Gm. of calcium chloride and 0.020 Gm. of sodium bicarbonate per hundred cubic centimeters.

6. Dr. Lewis D. Stevenson helped in the preparation and evaluation of the histologic slides.

greater (the average for 6 ears was 268 sq. cm. per hundred arteries per ear) than the area of the walls of the arteries from the control ears (the average for 6 control ears was 185.50 sq. cm. per hundred arteries per ear). This represents an increase in total area of 44 per cent over the control ears.

EXPERIMENTS WITH A VASOCONSTRICTOR SUBSTANCE

To ascertain whether a vasoconstrictor agent acts with equal promptness and to the same extent on thickened and on nonthickened arteries, the following experiments were performed. The vasoconstrictor agent, ergotamine tartrate, was chosen because it is an effective means of terminating an attack of migraine headache, and its use was, therefore, most relevant to this investigation.



Comparison of the effect of ergotamine tartrate on the control ear and on an ear infused previously for one hundred and twenty minutes with acetylcholine bromide (photograph taken by transillumination twenty-five minutes after injection of ergotamine tartrate).

A, control ear, showing striking vasoconstriction. Except for the marginal vessels, the blood vessels are barely visible. (The photograph of this ear, as compared with that of the infused ear (*B*), appears overexposed. This is because the exposure required for photographing the thickened, reddened infused ear was longer than was desirable for the thinner, pale control ear).

B, ear infused with acetylcholine bromide. The vasoconstriction was less evident, and the blood vessels were larger and more numerous than in the control ear.

Method.—Six cats were given infusions of acetylcholine bromide for two hours, as previously described, except that both ears were left in situ. Since the action of acetylcholine in the concentrations used is local and the agent is promptly destroyed, the ear on the infused side showed only the vasodilator effects of acetylcholine. The opposite, or control, ear retained its normal color and appearance. After two hours of infusion, ergotamine tartrate (0.007 mg. per kilogram) was injected into the femoral vein or subcutaneously, and the ears were inspected by transillumination and photographed.

Results.—Shortly after injection of ergotamine tartrate the control ear became pale and the vessels were notably constricted. The smallest vessels were no longer visible. In the infused ear the vasoconstriction began, or at least became noticeable, somewhat later. The time of vasoconstriction and the degree of constriction in the infused ear were variable. However, the infused ear remained redder than the control ear and its blood vessels significantly larger even after four hours! In 1 cat there was still a striking contrast between the arteries in the control ear and those in the infused ear after seven hours (figure).

COMMENT

From the data presented it is seen that cranial arteries exposed to the prolonged effect of the vasodilator agent acetylcholine bromide exhibit an increase in the thickness of the arterial walls. Thus, sustained dilatation of cranial vessels leads to transient structural changes. It is possible that the vasa vasorum in the dilated walls become more permeable and that the tissue spaces within the walls contain more fluid. The relation of these changes to clinical phenomena may be significant.

Dunning [7] collected the evidence concerning structural changes which he and others observed to be associated with attacks of migraine headache. In addition to prominent arteries, the defects outside the cranium include edema, ecchymosis, thrombosis and hemorrhage, and the defects within, thrombosis and hemorrhage. The facial edema and the results of hemorrhage may outlast the headache by many hours, or even days.

Changes in the appearance of capillaries have been observed during attacks of migraine headache.[8] These changes were attributed to swelling of the endothelial cells of the capillary wall [9] and to increased transudation.[8]

Kennedy [10] suggested that masses of fluid collected around intracranial blood vessels are responsible for both the migraine headache and the visual and other sensory disturbances. Kennedy's explanation is that the headache results from the rapidly formed "localized swellings" which stretch "agonizingly sensitive" meninges. This implies that during the attack of migraine the headache

7. Dunning, H. S.: Intracranial and Extracranial Vascular Accidents in Migraine, Arch. Neurol. & Psychiat. **48**:396 (Sept.) 1942.

8. Redish, W., and Pelzer, R. H.: Capillary Studies in Migraine: Effect of Ergotamine Tartrate and Water Diuresis, Am. Heart J. **26**:598, 1943.

9. Cohnheim, J. F.: Lectures on General Pathology, London, The New Sydenham Society, 1889.

10. Kennedy, F.: Migraine—A Symptom of Focal Brain Edema, New York State J. Med. **33**:1254, 1933.

precedes the visual defects because the fluid would be obliged to collect about the vessels before it could "irritate contiguous brain areas." As a matter of fact, however, visual disturbances usually precede the headache and end with its onset, or even before.

In short, there is no evidence that the edema associated with migraine is essential to the mechanism of either the preheadache or the headache phenomena. It may, however, modify the latter and manifest itself in other bodily effects, such as swelling of the face and extremities and disturbed urinary output.

The data thus far assembled have led us to the following formulation of the cranial mechanism concerned in the production of migraine: An initial local vasoconstriction of cerebral arteries produces visual and other sensory preheadache phenomena.[3] As these phenomena recede, vasodilator manifestations of headache appear. Sometimes the latter overlap the last traces of preheadache phenomena, and sometimes the headache begins after a short interval of freedom from symptoms. Rarely do the preheadache phenomena continue long after the headache has become established. The vasodilatation of certain cranial arteries, chiefly of one or another branch of the external carotid artery, gives rise to a throbbing, aching pain, which may be appreciably reduced by pressure on the common carotid artery, and sometimes on a superficial artery, and through the action of ergotamine tartrate. Vasodilatation when sustained during several hours leads to thickening or edema of the affected arterial wall and often to edema of adjacent tissue. Owing to transient thickening of their walls, the soft, readily collapsible arteries become rigid and pipelike. Further, the pulsating pain becomes a steady ache, and the artery itself becomes tender on palpation.

It has been demonstrated that ergotamine tartrate contracts a distended artery with thickened walls less promptly and completely than a normal one. Such differences in action indicate that ergotamine tartrate will be therapeutically most effective when administered soon after the onset of the attack of migraine headache.

CONCLUSIONS

After several hours of migraine headache changes in cranial arteries appeared. A distended temporal artery, for example, seems more prominent. It becomes more easily palpable through the skin, and, instead of being readily collapsible, is rigid and pipelike and is less easily compressed by the palpating finger. The nature of these alterations was studied by experimental induction of analogous changes in cats.

The structure of the arteries of the ears of 6 cats was studied after infusion for two hours of 10 cc. of mammalian Ringer solution containing 0.5 mg. of acetylcholine bromide per hundred cubic centimeters. Measurements demonstrated thickening of the arterial walls of the infused ears. Also, a vasoconstrictor agent, ergotamine tartrate, was observed to be less prompt and effective in constricting arteries with thickened walls than arteries with normal walls.

It is suggested that during attacks of migraine headache the cranial arteries involved may undergo similar changes after prolonged vasodilatation. Such changes may explain the rigid, pipelike texture of the arteries, the steady aching pain and the tenderness of these structures when headache has persisted for many hours. Also, these changes may explain the decreased ability of ergotamine tartrate to reduce promptly the intensity of prolonged headache.

525 East Sixty-Eighth Street.

CEREBRAL INJURY BY BLUNT MECHANICAL TRAUMA

SPECIAL REFERENCE TO THE EFFECTS OF REPEATED IMPACTS OF MINIMAL INTENSITY; OBSERVATIONS ON EXPERIMENTAL ANIMALS

C. G. TEDESCHI, M.D.

HARDING, MASS.

PURPOSE OF INVESTIGATION

It has been suggested by several investigators that the effects of cerebral trauma may be cumulative. As far back as 1874 Koch and Filene [1] had shown that animals could be killed by repeated small blows on the head without showing any evidence of structural damage to the brain. Later Martland [2] recognized a peculiar condition occurring among prize fighters, which he named "punch drunk" and which he attributed to the repeated head punishments they had suffered while in the ring. Then Shaller, Tamaki and Newman [3] showed the apparent increase in vulnerability of the cerebral vessels induced by the application of repeated blows. More recently Denny-Brown and Russell [4] demonstrated that paralysis of respiration of increasing duration and rise of blood pressure occurred with successive blows and that concussion could be obtained readily by repetition of moderately severe blows.

In apparent contrast to these observations are those of Noble and associates [5] leading to the concept of "trauma resistance"; by gradually increasing the amount of trauma they found that animals could tolerate a number of blows fatal to a normal animal. In explanation of this, biochemical analysis of the blood and tissues by Neufeld, Toby and Noble [6] seemed to indicate that the resistance which develops as a result of repeated trauma involves a stabilization of metabolic processes, which are notably upset in the "non-resistant traumatized animal."

As further knowledge along this line seemed desirable, experiments were planned with the aim of seeing whether the disorders of function observed by other investigators could be correlated with demonstrable changes in the nervous system. More exactly, one of the main points with which I was concerned in my investigation has been that of studying, under controlled experimental conditions, the immediate and delayed effects of repeated moderately severe blunt impacts on the heads of animals. The repeated impacts were delivered in two ways—to some animals at relatively short intervals and to others at longer intervals, the total amount of trauma being the same for the two groups.

In relation to the mechanism of trauma, brain injuries have been said to occur in one of the two following ways: by distortion of the skull or by movements of the brain within the skull. In view of the possibility of different effects from the two mechanisms of trauma, the results of the repeated impacts, both in close succession and at longer intervals, were studied comparatively: in animals in which a distortion of the skull, even of slight degree, was likely to occur under the force of the impact, and in animals in which forces of acceleration were mainly involved.

A blunt impact on the animal's head while at rest was thought to realize the first condition, while the second condition was made possible by a procedure which permitted a rapid acceleration of the head and its sudden arrest by meeting a resistance.

MATERIAL AND METHODS

The albino rat was chosen as the experimental animal, in view of the facility with which changes in behavior can be detected in this animal. Mature male and female rats of the same strain and approximately similar weights,

From the Laboratories of the Medfield State Hospital.

This paper was read at the May 1944 meeting of the Massachusetts Psychiatric Society.

1. Koch, W., and Filene, W.: Beiträge zur experimentellen Chirurgie, Arch. f. klin. Chir. **17**:190, 1874.

2. Martland, H. S.: Punch Drunk, J. A. M. A. **91**:1103 (Oct. 13) 1928.

3. Shaller, W. F.; Tamaki, K., and Newman, H.: Nature and Significance of Multiple Petechial Hemorrhages Associated with Trauma of the Brain, Arch. Neurol. & Psychiat. **37**:1048 (May) 1937.

4. Denny-Brown, D., and Russell, W. R.: Experimental Cerebral Concussion, Brain **64**:93 (Sept.) 1941.

5. Noble, R. L., and Collip, J. B.: Quantitative Method for Production of Experimental Traumatic Shock Without Hemorrhage in Unanaesthetized Animals, Quart. J. Exper. Physiol. **31**:187 (Feb.) 1942. Noble, R. L.: Development of Resistance by Rats and Guinea Pigs to Amounts of Trauma Usually Fatal, Am. J. Physiol. **138**:346 (Jan.) 1943.

6. Neufeld, A. H.; Toby, C. G., and Noble, R. L.: Biochemical Findings in Normal and Trauma-Resistant Rats Following Trauma, Proc. Soc. Exper. Biol. & Med. **54**:249 (Nov.) 1943.

ranging from 180 to 205 Gm., were used. During the course of the experiments they were properly fed, with all precautions to avoid the complications derived from a dietary deficiency. The weight of the animals was taken at the beginning and at the end of the experiment and was checked periodically in the intervening period. The animals which did not die spontaneously as a direct consequence of the trauma were killed by inhalation of chloroform, dying within a few seconds; several control animals, submitted to inhalation of chloroform alone, did not show any demonstrable lesion in the nervous system. As soon as the animal was dead, the head was severed from the body and placed in a 10 per cent solution of formaldehyde U.S.P. in isotonic solution of sodium chloride. After forty-eight hours, the skull was opened, and the cerebrum, the cerebellum, the two parafloccular lobes and the cervical portion of the spinal cord were removed in one block. A thorough inspection of the abdominal and thoracic organs was made in all animals. This seemed to be indicated particularly in the rats in which the changes in the brain did not explain sufficiently the course of events following the trauma. When observation with the naked eye did not reveal any noticeable change on which to focus further studies the brain was divided into two blocks in a horizontal plane, from the tip of the olfactory lobes to the base of the fourth ventricle, the section passing through the basal nuclei at equal distances from the vault and the base. The lower block comprised the base of the cerebral hemispheres, the pons and the cerebellum, and the upper block, the vault of the cerebral hemispheres.

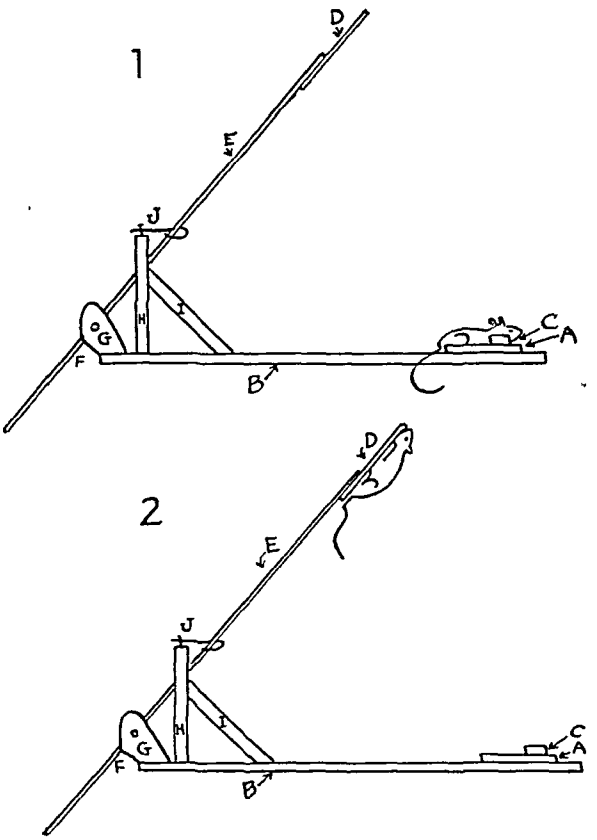


Fig. 1.—Platform (*A*) sliding in a slot (*B*) and provided with a block (*C*) shaped to the head of the animal; iron paddle (*D*), which can act either as a traumatizing agent or as a carrier of the animal; metal rod (*E*) passing through a revolving tumble block (*F*) set between two shoulders (*G*); upright block (*H*) reenforced by braces (*I*) and provided with a catch (*J*) to hold the rod and to release it suddenly.

One of the two blocks was embedded in paraffin, sectioned at different levels and stained with hematoxylin and eosin. From the other block frozen sections were made and stained according to the Cajal reduced silver method for nerve fibers, the Spielmeyer method for myelin sheaths, the Nissl method for nerve cells (cresyl violet) and the oil red O (pyridine solvent), sudan III and the Marchi method.

As the traumatizing agent, an apparatus was devised and set up [7] which consisted of two fundamental parts (fig. 1, *1* and *2*): first, a rectangular wooden platform (*A*), sliding in a slot cut in the base (*B*) and provided with a block (*C*) shaped to the head of the animal; and, second, a rectangular iron paddle (*D*) of sufficient weight and size to act either as a blunt traumatizing agent, in the procedure of compression concussion (fig. 1 A), or as carrier of the animal, in the procedure of acceleration concussion (fig. 1, *2*). The metal rod (*E*), attached to the iron paddle, was passed through a revolving tumble block (*F*) set between two shoulders (*G*), so as to allow the length of the rod to be adjusted as desired; the tumble block was supported by an upright (*H*), reenforced by braces (*I*) and provided with a catch (*J*) to hold the rod and to release it suddenly.

The possibility of reproducing by this apparatus injuries of the type most commonly occurring in man as a result of accidental head trauma is easily seen. When the iron paddle was allowed to fall and strike the fixed head of the animal lying stationary on the platform, the condition was realized of a moving object striking the head at rest, whereas the method of having the animal fixed to the falling paddle and striking the head against the platform realized the condition of a fall from a height on to a hard surface.

In preliminary experiments on a large number of animals, in which the amount of trauma was gradually increased, the momentum of the force necessary to produce the desired degree of trauma and, correspondingly, of injury to the brain, was determined exactly. For each degree of trauma, the effects of blows of identical strength were studied comparatively with each of the two mechanisms—moving head against stationary object and moving object against stationary head. With application of either mechanism, the following degrees of trauma were produced:

1. A crushing injury, with fracture of the skull, extensive damage to the brain and its involucres and death within three hours—immediate lethal blow (mass, 973 Gm.; velocity at point of impact, 392.8 cm. per second).

2. A less severe but still fatal injury, with or without fracture of the skull, with cerebral damage of various degrees and delayed death, within from four hours to seven days—delayed lethal blow (mass, 744 Gm.; velocity at point of impact, 367 cm. per second).

3. A concussive blow, with transient loss of consciousness [8] and apparently complete recovery in vary-

7. Dr. E. K. Holt and Dr. E. K. Holt Jr. gave assistance in this undertaking.

8. The presence or absence or defect of consciousness is a matter for conjecture in the experimental animal which cannot give any reliable test response as a human being does. When clear evidence of paralysis of cerebral functions was not obtainable, the loss of the pupillary reflexes was taken as a basic criterion of concussion. The absence of fracture of the skull or of gross hemorrhagic or necrobiotic change in the brain, brain stem or cervical portion of the spinal cord on postmortem examination was included as an additional basic criterion of concussion.

ing periods (mass, 567 Gm.; velocity at point of impact, 345.7 cm. per second).

4. A subconcussive blow, the strength of which was insufficient to cause loss of consciousness or any other immediate or delayed ill effects (mass, 453.6 Gm.; velocity at point of impact, 330.9 cm. per second).

It was this blow of minimal intensity which was used in the investigation of cumulative effects of repeated trauma.

Precautions were taken that all animals should receive a trauma of the same momentum each time and that the heads of the animals should be struck in the same region. The occipitoparietal region was chosen because in the rat this area of the skull is thicker and less liable to fracture.

In summarizing the protocols of the experiments, I shall proceed according to the degree of trauma, from the most to the least severe, in the following order[9]: (1) immediate lethal trauma (12 animals); (2) delayed lethal trauma (15 animals); (3) concussive trauma—maximum sublethal trauma (68 animals); (4) subconcussive trauma, not repeated (30 animals); (5) subconcussive trauma, repeated (*a*) at long intervals (60 animals, and (*b*) in close succession (60 animals).

Special consideration will be given in this study to the observations arising from the experiments on the animals of group 5.

TABLE 1.—*Effects of Immediate Lethal Trauma*

Rat No.	Time of Death	Skull	Postmortem Observations—Brain		Other Observations
			Site of Impact	Contralateral Injury	
			Moving Head Against Stationary Object		
17	2 hr.	Fracture	Small areas of hemorrhagic softening in both occipital lobes		
22	Immediate	Fracture	Extensive contused lacerations, with indriven fragments of skull	Subarachnoid hemorrhage at base	
21	Immediate	Fracture	Extensive contused lacerations, occipitocerebellar region	Subarachnoid hemorrhage at base	
23	3 hr.	Fracture	Extensive contused lacerations, with indriven fragments of skull	Subarachnoid hemorrhage at base	
18	10 min.	Fracture	Extensive contused lacerations	Hemorrhages in pontobulbar region	
16	3 hr.	Fracture	Small area of hemorrhagic softening, left temporoparietal region	.....	Edema of lungs
			Moving Object Against Fixed Head		
77	Immediate	None	Extensive contused lacerations	Subarachnoid hemorrhage at base	
12	Immediate	Fracture	Diffuse subarachnoid hemorrhage; small areas of hemorrhagic softening in both frontal lobes	Subarachnoid hemorrhage at base	
5	5 min.	Fracture	Extensive contused lacerations.....	.....	Hemorrhagic erosions in stomach
6	8 min.	None	Extensive contused lacerations.....	.....	Hemorrhagic erosions in stomach
13	10 min.	Fracture	Extensive contused lacerations.....		
7	3 hr.	None	Diffuse subarachnoid hemorrhage; hemorrhagic softening, occipitoparietal region		

SURVEY OF EXPERIMENTS

IMMEDIATE LETHAL TRAUMA

Gross Observations.—The results of postmortem examination of the animals dying immediately or shortly after a crushing type of injury had been applied are graphically represented in table 1, and figure 2 shows the amount of cerebral damage suffered by the animals of this group. Fracture of the skull was found in almost all the rats, and in 2 animals (rats 22 and 23) fragments of skull were found deeply driven in the brain matter. Contusions and extensive bruising of the cortex, including several adjacent convolutions and involving to a considerable degree the underlying white substance, were outstanding features in all cases, without any differences that could be related to the mechanism of trauma. As Rand and Courville[10] have proposed, lesions of this type might be properly defined as "contused lacerations," thus emphasizing the role played by the blood flooding from the ruptured blood vessels in destroying and hollowing large areas of brain.

Contralateral injury, in the sense that a pole of the brain opposite the site of impact showed evidence of damage, was found in 1 animal only (rat 18); contralateral subarachnoid bleeding was, on the contrary, frequent, as the result of the tearing of the delicate vessels entering the base of the brain.

In this group an animal (rat 16) is included which died in the third hour, after the development of acute pulmonary edema. As the cerebral damage was rather limited in this animal, consisting of a small area of hemorrhagic softening in the left temporoparietal region, the impression was that the superseding pulmonary edema had

9. The animals used in the preliminary experiments (150 approximately) to establish the momentum of the force necessary to produce the different degrees of trauma are not included.

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

rendered fatal what otherwise would have been a reparable injury to the brain.

Among the subsidiary findings, the presence of blood in the stomachs of 2 animals (rats 5 and 6) deserves mention. In both animals the gastric mucosa showed a scattering of tiny hemorrhages, which had a tendency to aline themselves along the crests of the gastric plicae. The hemorrhages were in general superficial, and as the mucosa was not depressed or otherwise altered, the resulting pattern was that of a simple hemorrhagic change.

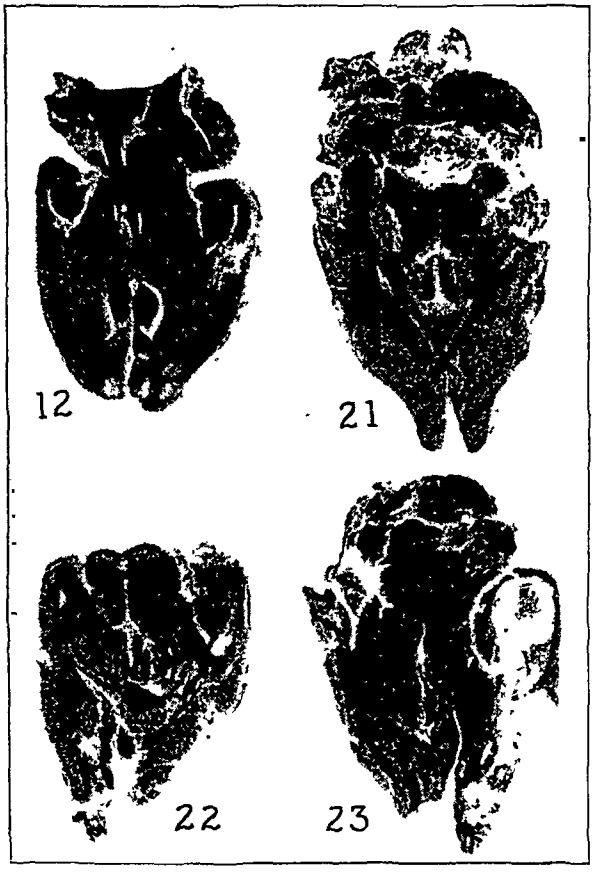


Fig. 2.—Horizontal sections of the brains of 4 animals which died shortly after a crushing type of injury (immediate lethal trauma), showing extensive contused lacerations. Rats 21, 22 and 23 struck the moving head against the stationary object; rat 12 was struck by the moving object on the stationary head. Fracture of the skull was a constant finding in all cases, and in 2 animals (rats 22 and 23) fragments of skull were found driven deeply in the brain matter.

With the exception of 1 animal that received the blow without showing loss of consciousness but shortly thereafter became comatose and died in the third hour, all the animals of the group were made unconscious at the time of the trauma and did not recover before death.

Microscopic Observations.—As one would expect, no evidence of progressive change was seen in the microscopic sections of the brains of the animals dying outright after the trauma. At the site of the hemorrhages there was almost complete obliteration both of cells and of fibers; and when fibers were still recognizable, they appeared twisted, fragmented and widely separated one from another by the interposed extravasated blood.

Progressive changes in nerve fibers, on the other hand, were already present in the animals surviving the trauma from two to three hours. In the hemorrhagic areas some of the nerve fibers stained poorly; others were deeply impregnated, and still others appeared to be thickened, with interruptions which at times resolved themselves into granular formations (fig. 3 *A*). Granular disintegration and twisting of fibers, with peculiar zigzag figures and terminal swelling of the ends of the fragmented fibers (bulbs of retraction), were also noticeable in the immediate vicinity of the hemorrhagic areas and at times in remote areas of the brain, otherwise undamaged (fig. 3 *B*). The lesions in the axis-cylinders were accompanied by evidence of disintegration of the myelin sheaths, which already at the second hour displayed varicose swelling, moniliform thickening, with reabsorption in areas, and formation of ellipsoids and fatty droplets (fig. 3 *C*). Clublike formations at the ends of the degenerated portions of interrupted fibers were noticeable in the myelin preparations, and they seemed to correspond to the bulbs of retraction of the fragmented axons in the silver-impregnated sections.

All these findings are in agreement with previous observations by other authors (Jakob,[11] Pfeifer,[12] Schwartz and Fink,[13] Rand and Courville,[10] Greenfield,[14] Hassin[15]) and lend further support to the recent conclusion of Rowbotham[16] that "demonstrable changes in neurons, other than in contusional areas, can always be found following fatal (head) injuries."

11. Jakob, A.: Ueber die feinere Histologie der sekundären Faserdegeneration in der weissen Substanz des Rückenmarks, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1912, vol. 5, p. 1; Experimentelle Untersuchungen über die traumatischen Schädigungen des Zentralnervensystems, ibid., vol. 5, p. 182.

12. Pfeifer, B.: Ueber die traumatische Degeneration und Regeneration des Gehirns erwachsener Menschen, J. f. Psychol. u. Neurol. **12**:96, 1908.

13. Schwartz, P., and Fink, L.: Morphologie und Entstehung der geburtstraumatischen Blutungen im Gehirn und Schädel der Neugeborenen, Ztschr. f. Kinderh. **40**:427, 1925.

14. Greenfield, J. G.: Some Observations on Cerebral Injuries, Proc. Roy. Soc. Med. **32**:43 (Nov.) 1938.

15. Hassin, G. B.: General Pathological Considerations in Brain Injury, in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1940, chap. 2.

16. Rowbotham, G. F.: Acute Injuries of the Head, Baltimore, Williams & Wilkins Company, 1942.

Fig. 3.—*A*, twisting and fragmentation of nerve fibers in a subcortical area of contused laceration. The animal, rat 7, died three hours after a severe blow on the stationary head which had left the skull intact (immediate lethal trauma). Cajal stain; ocular 4; objective 10.

B, thickening, spiroid course and splitting and fragmentation of nerve fibers in a portion of brain, apparently undamaged, at some distance from the area of contusion shown in *A*. Cajal stain; ocular 4; objective 10.

C, from a section at a level corresponding to that of sections *A* and *B*, showing severe disintegration of myelin with formation of ellipsoids and fat droplets. Spielmeyer stain; ocular 4; objective 40.

In the study of the sections in this figure, and of those in figures 4, 9, 10, 11, 12, 13 and 14, a Bausch & Lomb microscope was used.

DELAYED LETHAL TRAUMA

The longer period of survival, from four hours to seven days, of the animals of this group, which were submitted to a trauma of less intensity, and the lesser magnitude and depth of the cerebral damage justify a separate description. As is graphically represented in table 2, only 3 animals showed evidence of fracture of the skull. At the site of impact the cerebral damage varied from a more or less extensive subarachnoid hemorrhage to contused laceration of the brain substance, involving at times several contiguous convolutions. Opposite the zone of impact evidence of contralateral injury was found in 4 rats; in 2 animals the damage consisted of subarachnoid hemorrhage, while in 2 others a dissemination of tiny hemorrhages was noticeable in the pons and the bulbar region. With respect to the two mechanisms of trauma, no differences were noticed in the apparent effects with blows of equal intensity.

In 7 of 15 animals, postmortem examination of the brain failed to reveal any change that could be detected with the naked eye. The examination of these animals was extended to large portions of the spinal cord, which also appeared grossly intact. In 2 of these rats acute bilateral pulmonary edema accounted, very likely, for the sudden death, which occurred at the eighth and the twenty-fourth hour after an apparently good recovery from a short period (five to ten minutes) of unconsciousness following the trauma. A condition of shock was suspected in 2 other animals which lost consciousness after the trauma, did not regain it completely and died at the fourth and fifth hours respectively, showing pronounced congestion of the abdominal organs. In the remaining 3 animals the postmortem observations did not offer any plausible explanation to account for the fatal outcome.

Microscopic Observations.—It was mainly on the brains of these 7 rats that the histologic study was focused. Changes in the nerve cells, axis-cylinders and myelin sheaths, which at times represented the only signs of local damage, less frequently accompanied by evidence of tissue edema, were revealed in the microscopic sections from all these apparently undamaged brains. Such changes were not diffuse but were focal in distribution, areas which appeared entirely normal alternating in the same field with others displaying more or less severe disintegration of neurons. This disintegration could be followed in its progressive stages according to the period of survival of the animal. In the animals which died from the fourth to the eighth hour the cortical nerve cells here and there appeared swollen, with huge cytoplasmic vacuoles which had a tendency to aline themselves at the periphery of the cell bodies. The apical dendrites were thickened, either diffusely or in limited tracts, and tortuous, with curvatures of varying depths and with a corkscrew twisting that contrasted sharply with the linear course of undamaged axis-cylinders nearby. Other cells showed absence of expansions (aneuritic cells), whereas still others

TABLE 2.—*Effects of Delayed Lethal Trauma*

Rat No.	Time of Death	Skull	Postmortem Observations—Brain		Other Observations
			Site of Impact	Contralateral Injury	
			Moving Head Against Stationary Object		
72	4 hr.	.....	Not remarkable.....	.....	Congestion of abdominal organs
71	5 hr.	.....	Not remarkable.....	.....	Congestion of abdominal organs
1	15 hr.	.....	Not remarkable.....	.....	.....
22	6 hr.	Fracture	Contused laceration of occipitotemporal region	Subarachnoid hemorrhage at base	
23	4 hr.	Fracture	Contused laceration of occipitocerebellar region	Subarachnoid hemorrhage at base	
30	8 hr.	.....	Not remarkable.....	.....	Pulmonary edema
2	24 hr.	.....	Not remarkable.....	.....	Pulmonary edema
11	24 hr.	.....	Subarachnoid hemorrhage.....	Hemorrhages in pontobulbar region	Pulmonary edema
9	5 days	.....	Small area of softening in frontal region		
8	7 days	.....	Occipital subarachnoid hemorrhage	.....	Hemorrhagic erosions in stomach
			Moving Object Against Stationary Head		
95	4 hr.	Fracture	Diffuse subarachnoid hemorrhage	Hemorrhages in pontobulbar region	
78	19 hr.	.....	Diffuse subarachnoid hemorrhage		
80	3 days	.....	Not remarkable.....		
85	5 days	.....	Not remarkable.....		
81	5 days	.....	Occipitotemporal subarachnoid hemorrhage		

exhibited granular tracts which outlined the course of the disintegrated dendrites. Changes of the same type were seen in the medullated axons, which in some places displayed varicose swelling or fragmentation, with bizarre end bulbs of various sizes and occurring mostly as small balls or spirals. The changes in the axis-cylinders were accompanied by changes of corresponding severity in the myelin sheaths, which had a moniliform appearance, narrow segments alternating with fusiform or ovoid swellings of various sizes. Evidence of more advanced disintegration of myelin was shown by the animals surviving the effects of the trauma longer—from nineteen hours to seven days. It consisted of conglomerates of fat droplets, which had a tendency to assume a linear distribution along the damaged axons. The latter appeared mostly as granular remnants with balls here and there, at times free and at times still attached to the ends of the degenerated portions of interrupted fibers. When the evidence of damage was most severe, bizarre-shaped scavenger cells, containing fat globules, were noticeable.

CONCUSSIVE TRAUMA (MAXIMUM SUBLETHAL TRAUMA)

Sixty-eight animals received a single blow on the head that made them unconscious for a period varying from ten seconds to fifteen minutes, followed by recovery. These 68 animals were divided into two groups, half being made to strike the moving head against the stationary object and the other half being struck on the stationary head by a force of exactly the same momentum. With blows of identical strengths, no differences were noted in the effects with the two mechanisms of trauma.

Some of the animals were killed shortly after the trauma, from one hour to seventy-two hours, in order to detect any early organic changes. Others were kept under observation for two months and then killed. During this period the great majority of the animals did not reveal any evidence of abnormal psychomotor behavior. Only 4 rats showed decreased activity and progressive loss of weight, estimated at the end of the experimental period to be about 30, 38, 42 and 45 Gm. respectively.

Microscopic Observations.—In all animals but 1, in which petechial hemorrhages were found both in the pons and in the bulbar region, gross inspection of the brains, and even of the sections stained with hematoxylin and eosin, failed to reveal any demonstrable changes except for occasional vascular engorgement and doubtful signs of edema of the brain matter. Changes in nerve cells, axis-cylinders and medullary sheaths were seen, however, when the stains proper for the nerve tissue elements were applied.

In the Cajal silver-stained preparations of the brains of animals killed one and two hours after the trauma, the apical dendrites appeared thickened, with a somewhat spiral course and at times a definite corkscrew shape (fig. 4 *B*). The corresponding nerve cells in the Nissl preparations showed loss of clearness of cell outlines, swollen cytoplasm and tigrolysis, with displacement of the nucleus to the periphery of the cell body (fig. 4 *A*). These changes were not diffuse, as groups of cells with evidence of damage alternated with others displaying normal cellular patterns and axis-cylinders pursuing their usual straight course. The same type of focal change was displayed by the medullated axons, some of which appeared poorly impregnated, varicose and swollen, in contrast to other axons which were overstained with the reduced silver (fig. 4 *C*). Still other fibers showed twisting; and when two or three of these twisted fibers lay close together, they gave rise to peculiar loops and spirals, to which corresponded a moniliform thickening or a fusiform swelling of variable size in the myelin-stained preparations (fig. 4 *D*).

More advanced myelin disintegration and neurolysis were noticeable in the animals killed from the fourth to the seventy-second hour. Conspicuous corkscrew twisting of the axis-cylinders was still recognizable in sparse areas, but more frequently in these animals the location of the axis-cylinders was indicated by irregular fragments, at times ending in blunt-tipped bulbs, and by tail-like rows of disappearing granules. The changes in the axis-cylinders corresponded fairly well, both in severity and in distribution, to those in the myelin sheaths. Individual myelin sheaths in the process of disintegration appeared swollen, thickened and fragmented, with reabsorption in areas and resolution into round, oval or irregularly shaped fat globules. The fat globules lay for the most part free in the tissue; to a less extent they were contained within compound granular corpuscles.

Of the animals killed after two months, none showed at postmortem examination any grossly detectable evidence of the previous trauma. In the majority of the animals microscopic study of the sections also failed to reveal any significant change. Microscopic examination of the brain sections of the 4 rats which had shown decreased activity and progressive loss of weight after the trauma revealed, on the contrary, rarefaction of nerve cells in disseminated zones of the cerebral cortex and small areas of demyelination in the subcortical white matter, with almost complete obliteration of axis-cylinders and evidence of free

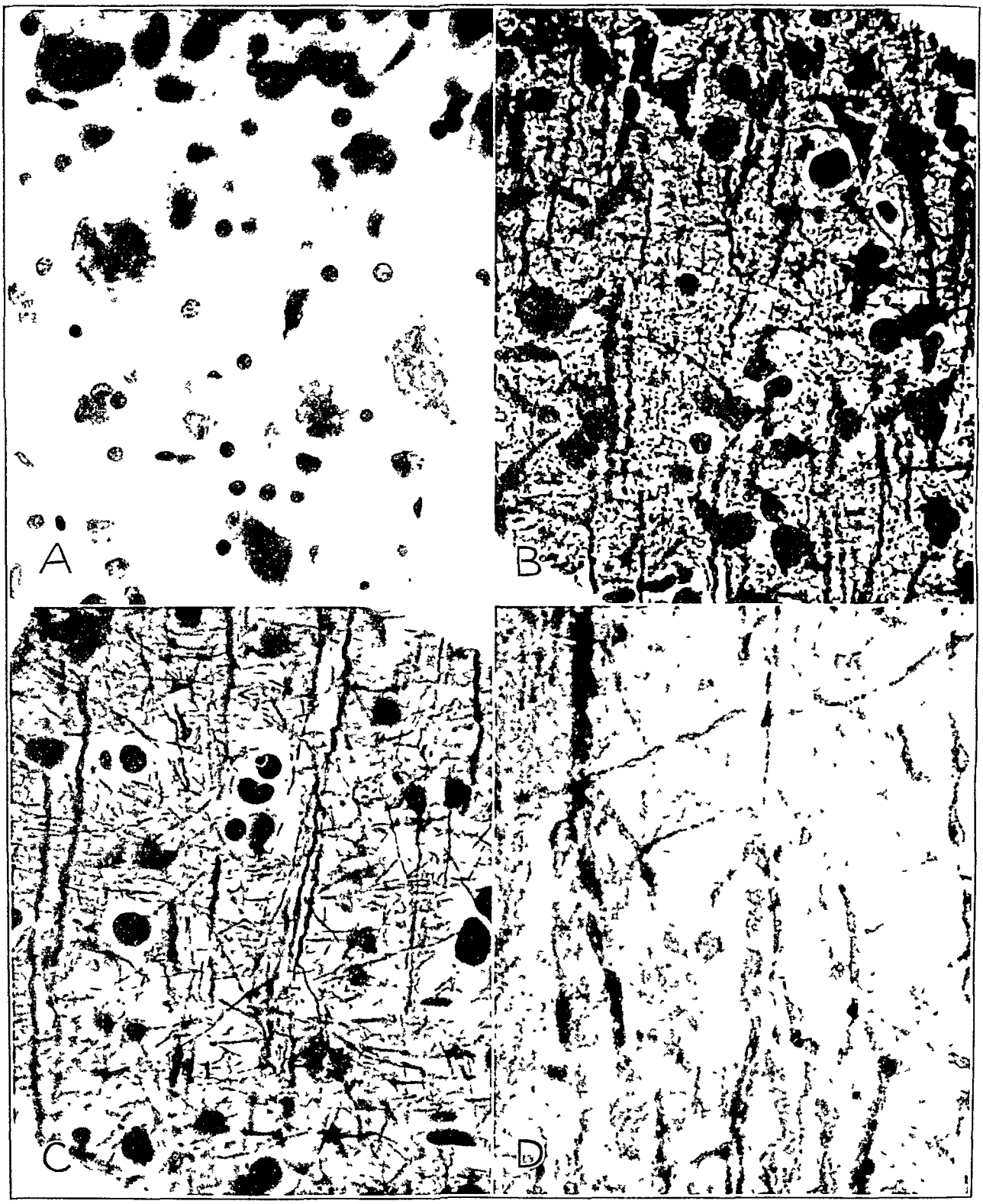


Fig. 4.—*A*, swelling, tigrolysis and pericellular edema of cortical nerve cells in a rat (no. 4) killed one hour after a concussive blow of moderate intensity (immediate lethal trauma)—moving head struck against stationary object—which had made it unconscious for five minutes and had left the skull and brain apparently intact. Nissl stain; ocular 6; objective 40.

B, from a Cajal preparation at a level corresponding to that of *A*, showing pronounced thickening, corkscrew twisting and occasional fragmentation of the apical dendrites. Ocular 4; objective 40.

C, medullated axons in the white matter of the perithalamic region, showing flexuous aspect, overstaining and at times spiroid course and fragmentation. Cajal stain; ocular 4; objective 40.

D, swelling, moniliform thickening and incipient breaking down of myelin sheaths in the same area of the brain. A few fairly well preserved myelin sheaths are still recognizable in the field. Spielmeyer stain; ocular 6, objective 40.

balls in the corresponding areas. In the parts that were damaged there was hyperplasia of astrocytes, which did not seem to be accompanied with an appreciable increase of glial fibers.

SINGLE SUBCONCUSSIVE TRAUMA

The term subconcussive is here applied to a trauma of such minimal strength as to be insufficient to cause loss of consciousness or any other apparent immediate or delayed effect in a normal animal. Thirty rats, divided into two equal groups, were submitted to this trauma; in one group the moving head was made to strike the stationary object and in the other the moving object struck the fixed head. All animals were killed at intervals of from one hour to forty days after the trauma, and none of them showed either gross or microscopic evidence of lesions.

REPEATED SUBCONCUSSIVE TRAUMA AT LONG INTERVALS

Cumulative effects, as revealed by temporary loss of consciousness, at times followed by death or by persisting functional disorders,[17] were shown with a certain frequency when a trauma of the same strength as the one used in the previous experiment was repeated at intervals of from two to six days, with a total of fifteen blows delivered in a fifty day period. As shown in table 3, both groups of animals, the rats striking the moving head against the stationary object (A) and the rats with the stationary head struck by the falling hammer (B), showed evidence of ill effects under the increasing trauma, but the frequency differed in the two groups. Already at the third and the fourth blow, respectively, in the two groups a few animals began to lose consciousness, and their number increased steadily under the successive blows. At the end of the experiment 57 per cent of the animals of group A had been made unconscious; of these, 7 per cent showed persisting functional disorders, and 17 per cent died as a direct consequence of the trauma. The incidence of ill effects was somewhat lower in the animals of group B, with only 40 per cent showing temporary loss of function, none dying and 10 per cent showing persisting functional disorders, while the majority, 60 per cent, went through the entire experimental period without displaying any immediate or late effects of the repeated trauma.

In most instances, once the animal had begun to lose consciousness, concussive effects occurred with each successive blow. A limited number of animals, however, which had been made unconscious by a previous blow failed to reveal any immediate ill effects from the next blow, to become unconscious again at a later blow.

The period of unconsciousness varied in the different animals each time from transient loss of the corneal reflexes to a more extensive paralysis of functions, lasting from a few minutes up to one hour. There was no apparent correlation between the number of blows and the duration of the state of unconsciousness.

Of the symptoms of abnormal behavior occasionally developing as the result of the repeated trauma, the most apparent was an unusual stiffness in the posture of the animal, interrupted at times by spells of more or less generalized trembling. The animals responded slowly to all types of external stimulation and often refused to eat, the result being a rapid decrease in body weight. When made to walk, they showed unsteady gait and a somewhat uncertain equilibrium, and at intervals flopping of one leg. Later, distinct dragging of the legs developed, with general slowing down of muscular movements. In general, once these symptoms had started, they showed a tendency to progress rapidly and then to remain stationary, having reached a certain level (observations up to the one hundred and twentieth day). All animals affected in this way had been made unconscious in the course of the experiment. No definite correlation could be seen, however, between the duration of the loss of consciousness at the moment of impact and the symptoms of abnormal behavior developing later, as they were seen both in the animals which had shown immediate evidence of severe concussion and in animals in which the only sign of concussion had consisted in transient loss of corneal reflexes.

IN CLOSE SUCCESSION

In contrast to the animals of the previous experiment, which received the blows at long intervals, the animals in this experiment received the blows in close succession, one after another, at intervals of approximately one minute. In this experiment, at the first evidence of concussion the animal was released, and in no case was the experimental period protracted beyond fifteen blows. As seen in table 4, a small number of animals in each of the two groups (A, the rats striking the moving head against the stationary object, and B, the rats with the fixed head struck by a moving object) were already unconscious at the end of the fifth blow, additional animals being made unconscious with the succeeding blows. At the end of the experimental period

17. The words "functional disorder" are used here in their proper sense, to indicate a "disorder of function of the brain." They are not used in the common clinical sense, in which they often have a "psychogenic" connotation.

73 per cent of the animals of group A had been made unconscious, in contrast to 40 per cent of group B. Most of the animals made unconscious under the repeated trauma showed a disorders developed, namely, in 13 and 10 per cent, respectively, of the two groups. These symptoms, which were fairly similar to those described in the previous experimental groups,

TABLE 3.—*Effects of Repeated Subconcussive Trauma Given Two to Six Days Apart.**

Rat No.	Number of Blows 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Persisting Functional Disorders
							A. Moving Head Against Stationary Object									
138	—	—	U-5"†	—	U-15"	—U-2'	U-20"	U-4'	U-5'	U-10"	U-2'	U-5'	U-4'	U-20'	U-45'	
139	—	—	—	U-2"	U-10"	—	U-8"	U-Died at 24 hours								
33	—	—	—	U-10'	U-1'	U-2'	U-2'	U-4'	U-10'	U-20'	Procedure discontinued.....					Began at 7th blow
40	—	—	—	—	U-2"	U-5"	U-2'	U-1'	Died in 1 hour							
36	—	—	—	—	U-4"	U-2'	U-Died in 1 hour									
41	—	—	—	—	U-2"	U-3"	U-3"	U-10'	U-15'	U-Died in 2 hours.....						Began at 8th blow
34	—	—	—	—	—	U-3"	U-2"	U-1'	U-2"	U-10'	U-4'	—	U-10'	U-18'	U-60'	
27	—	—	—	—	—	U-3"	U-4"	U-5"	U-10'	U-20"	U-5'	U-4'	U-3'	U-12'	U-30'	
35	—	—	—	—	—	—	U-2'	U-Died at 24 hours								
32	—	—	—	—	—	—	—	U-3'	U-7'	U-15'	U-8'	U-20'	U-5'	U-2'	U-10'	
38	—	—	—	—	—	—	—	U-2"	U-3"	U-1'	—	U-4'	U-7'	U-5'	U-12'	
29	—	—	—	—	—	—	—	—	U-2"	U-2'	U-3'	U-7'	—	U-10'	U-5'	
39	—	—	—	—	—	—	—	—	—	U-2'	U-1'	—	U-3'	U-5'	U-6'	
31	—	—	—	—	—	—	—	—	—	U-3'	—	—	U-6'	U-4'	U-8'	
131	—	—	—	—	—	—	—	—	—	U-8'	U-2'	U-5'	U-40"	P-7'	U-10'	
141	—	—	—	—	—	—	—	—	—	—	—	—	—	U-10'	U-60'	
133	—	—	—	—	—	—	—	—	—	—	—	—	—	—	U-5'	
42	—	—	—	—	—	—	—	—	Procedure discontinued.....							Control
37	—	—	—	—	—	—	—	—	—	—	Procedure discontinued.....					Control
43																
134																
135																
136																
137																
140	No immediate or delayed effects (15 blows)															
142																
132																
44																
49																
143																
							B. Moving Object Against Stationary Head									
168	—	—	—	U-5'	U-3'	—	U-10"	U-5'	U-20"	U-6'	Procedure discontinued.....					Began at 5th blow
89	—	—	—	U-5"	—	—	—	U-10"	U-5'	U-20'	Procedure discontinued.....					Began at 9th blow
91	—	—	—	—	U-5"	—	—	U-1'	U-2'	U-10'	—	U-30"	U-5'	U-8'	U-12'	
171	—	—	—	—	U-5"	—	U-2'	U-5'	U-30"	U-10'	—	—	U-1'	U-15'	U-13'	
177	—	—	—	—	U-10"	U-2'	—	U-10'	U-15'	U-5'	—	U-20"	U-2'	U-30"	U-6'	
184	—	—	—	—	—	—	—	U-10"	U-50"	U-15'	U-3'	—	U-7'	U-2'	U-5'	
186	—	—	—	—	—	—	—	U-20"	U-1'	U-5'	U-2'	U-4'	U-1'	U-10'	U-20'	
88	—	—	—	—	—	—	—	U-3"	U-5'	U-60'	Procedure discontinued.....					Began at 10th blow
163	—	—	—	—	—	—	—	—	U-10"	U-5'	U-40"	U-2'	U-5'	—	U-10'	
164	—	—	—	—	—	—	—	—	U-15"	U-20'	—	U-4'	U-6'	U-50"	U-8'	
182	—	—	—	—	—	—	—	—	—	—	—	U-20"	—	U-2'	U-3'	
173	—	—	—	—	—	—	—	—	—	—	—	—	—	U-5'	U-9'	
90	—	—	—	—	—	—	—	—	—	—	Procedure discontinued.....					Control
87	—	—	—	—	—	—	—	—	—	—	Procedure discontinued.....					Control
86																
165																
166																
167																
169																
170																
172																
174																
175	No immediate or delayed effects (15 blows)															
176																
178																
179																
180																
181																
183																
185																

C. The Two Mechanisms of Trauma

Animals Which Were Made Unconscious, Had Persisting Functional Disorders or Died, with the Two Mechanisms of Trauma

Procedure	Unconsciousness	Persisting Functional Disorders	Death (Within 29 Days)	No Apparent Effects
Moving head, stationary object.....	57%	7%	17%	43%
Moving object, stationary head.....	40%	10%	0	60%

* In this table, and in table 4, the data for the blow employed were as follows: mass, 453.6 Gm.; velocity, 330.9 cm. per second; kinetic energy, 1.83.

† U indicates unconsciousness, measured in seconds or minutes.

prompt and apparently complete recovery; a few fatalities occurred, however, in both groups of animals, with an incidence of 17 per cent in group A and of 7 per cent in group B, while in a few others persisting symptoms of functional appeared shortly after the trauma in some animals and several days or weeks later in other animals. All animals displaying persisting evidence of abnormal behavior had received a large number of blows. This was true, for instance,

TABLE 4.—*Effects of Subconcussive Trauma, Repeated in Close Succession*

Immediate and Late Results	No. Blows	No. Animals	Total
A. Moving Head Against Stationary Object			
Unconsciousness....	1-5	3	22 (73%)
	6-10	8	
	11-15	11	
Late functional disorders			4 (13%)
Death (within 29 days)...			5 (17%)
No apparent effects			8 (27%)
B. Moving Object Against Stationary Head			
Unconsciousness....	1-5	2	12 (40%)
	6-10	3	
	11-15	7	
Late functional disorders			3 (10%)
Death (within 29 days)...			2 (7%)
No apparent effects			18 (60%)

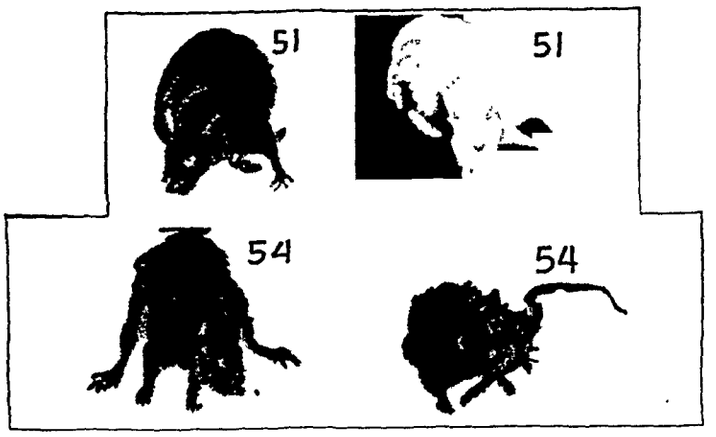


Fig. 5.—Locomotor disorders in 2 rats, as they appeared ten days after the trauma. Rat 51 had received thirteen subconcussive blows in close succession (moving head struck against stationary object) and was unconscious for about ten minutes. Rat 54 received fifteen subconcussive blows in close succession (moving object striking against stationary head) and was unconscious for a few seconds. Evidence of psychomotor disorders developed in both animals a few days after the trauma.

of the 2 rats, 51 and 54, shown in figure 5, which received thirteen and fourteen blows, respectively —rat 51 by the procedure of striking the moving head against the stationary object and rat 54 by the procedure of the moving object striking the stationary head. Rat 51 was unconscious for about ten minutes; rat 54, for a few seconds. Both began to show unsteady gait and general slowing down of muscular movements a few days after the trauma. One died at the twenty-ninth day of the experiment, and the other was killed at the thirty-fifth day because it was extremely emaciated and unable to eat. The symptoms presented by these 2 animals, and by the others similarly affected, are suggestive of the symptoms described in human beings as among the late results of repeated head injuries apparently of a minor type (Martland [2]); the comparison, however, for obvious reasons, cannot be pursued further.

The effects of repeated subconcussive blows in close succession—one minute apart—and at intervals of two to six days, under the two mechanisms of trauma are compared in table 5. With respect to the interval between blows no remarkable differences are seen in the group of animals struck by the moving object on the stationary head. With the other mechanism of trauma, the animals which had received the blows in close succession showed a higher incidence of unconsciousness than the animals which had received the repeated trauma at longer intervals.

TABLE 5.—*Comparative Effects of Repeated Subconcussive Blows Delivered in Close Succession and at Intervals According to the Two Mechanisms of Trauma, as Shown by the Percentage of Animals Which Were Made Unconscious, Showed Persisting Functional Disorders or Died (Within Twenty-Nine Days)*

Procedure	Unconsciousness	Persisting Functional Disorders	Death (Within 29 Days)	No Apparent Effects
A. Moving Head Against Stationary Object				
Blows repeated in close succession.....	73%	13%	17%	27%
Blows repeated at intervals (2-6 days)..	57%	7%	17%	43%
B. Moving Object Against Stationary Head				
Blows repeated in close succession.....	40%	10%	7%	60%
Blows repeated at intervals (2-6 days)..	40%	10%	0	60%

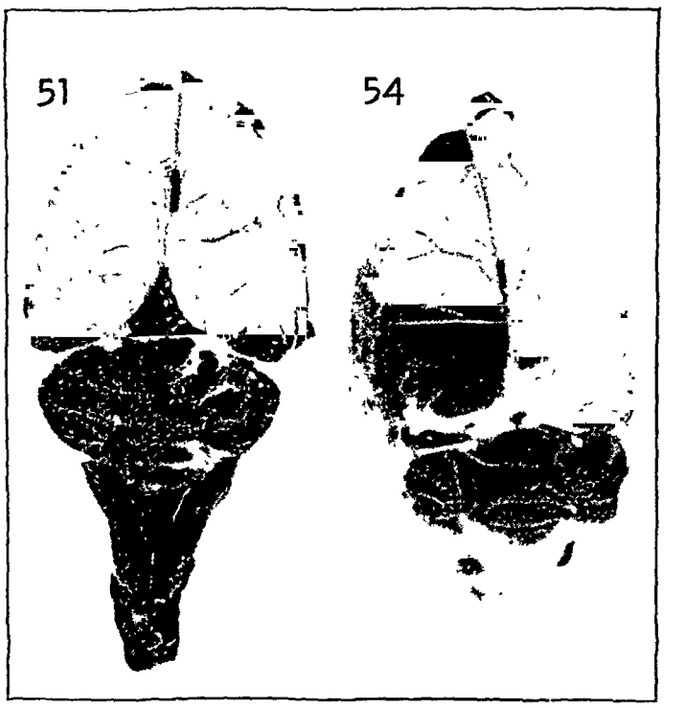


Fig. 6.—Gross appearance of the brains of 2 animals (rats 51 and 54) which had displayed pronounced psychomotor disorders during life, as shown and described in figure 5. No evidence of abnormality is seen in either brain.

Postmortem Observations.—In an investigation of a possible relation between the symptoms presented by the animals during life and the postmortem changes, the question arises whether the animals that stood the repeated trauma, given either at long intervals or in close succession, without showing any apparent immediate or late ill effects suffered an amount of damage different from that exhibited by the animals which were made unconscious, once or repeatedly, or which displayed any other evidence of post-traumatic functional disorders.

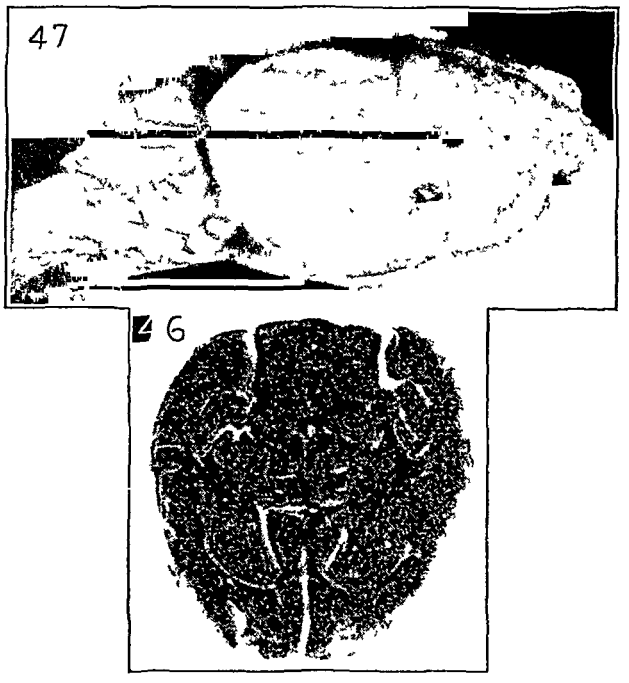


Fig. 7.—*A*, lateral view of the brain of rat 47, showing two punctate hemorrhages in the right temporal lobe. This animal was unconscious for five minutes after receiving fifteen blows in close succession (moving head struck against stationary object) and died twenty-four hours later, of acute generalized pulmonary edema. The skull was intact.

B, horizontal section of the brain of rat 46, revealing dissemination of tiny petechial hemorrhages of the ring type both in the cortex and in the white matter. This animal was unconscious for twenty minutes after receiving fifteen blows in close succession (moving head struck against stationary object) and died forty-eight hours later. The skull was intact.

In order to investigate as far as possible eventual correlations between disorders of function and histologic changes, when an animal which had shown such disorders died or was killed another animal apparently unaffected by trauma of identical type, intensity and frequency was killed at the same time, and the histologic sections of the brains of the 2 animals were closely compared at corresponding levels. As far as could be judged from the material examined, in most of the animals there was a certain relation between the response to the trauma during life and the amount of cerebral damage, as the latter appeared to be least severe in the animals which were clinically unaffected and became progressively more severe as the animals were made unconscious repeatedly, manifested persisting functional disorders or died as the result of the repeated trauma.

In the great majority of the animals postmortem examination did not reveal any deviation from the normal that could be detected with the naked eye. This is true, for instance, of the 2 brains represented in figure 6, from rats 51 and 54, which had displayed conspicuous psychomotor disorders during life. Gross evidence of injury to the brain, however, was seen in a few animals—in 7 of 120 animals submitted to the repeated trauma. In 1 animal, rat 46 (fig. 7), which was unconscious for about twenty minutes after receiving fifteen blows in close succession and died four days later, after an apparently good recovery, dissemination of petechial hemorrhages of the ring type, both in the cortex and in the white matter, was noted on horizontal

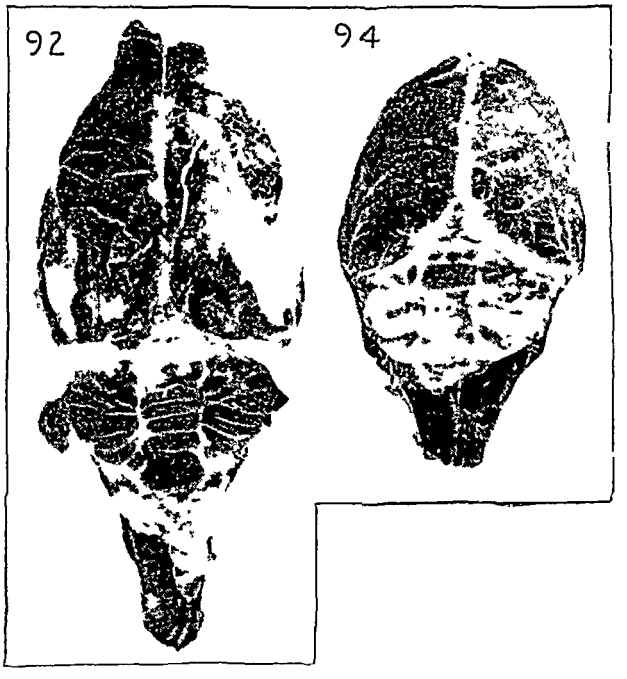


Fig. 8.—*A*, superior view of the brain of rat 92, showing extensive subarachnoid hemorrhages in the temporoparietal regions of both hemispheres, in the cerebellum and in the brain stem. The animal was unconscious for about one hour after receiving nine subconcussive blows in close succession on the stationary head and died seven days later. There was no evidence of fracture of the skull.

B, superior view of the brain of rat 94, showing a thin layer of clotted blood between the cerebellum and the meninges. This animal was made unconscious by fifteen blows in close succession on the stationary head and died four days later. The skull was intact.

section of the brain, the bleeding points being most numerous in the white substance; there were concomitant hemorrhagic erosions in the

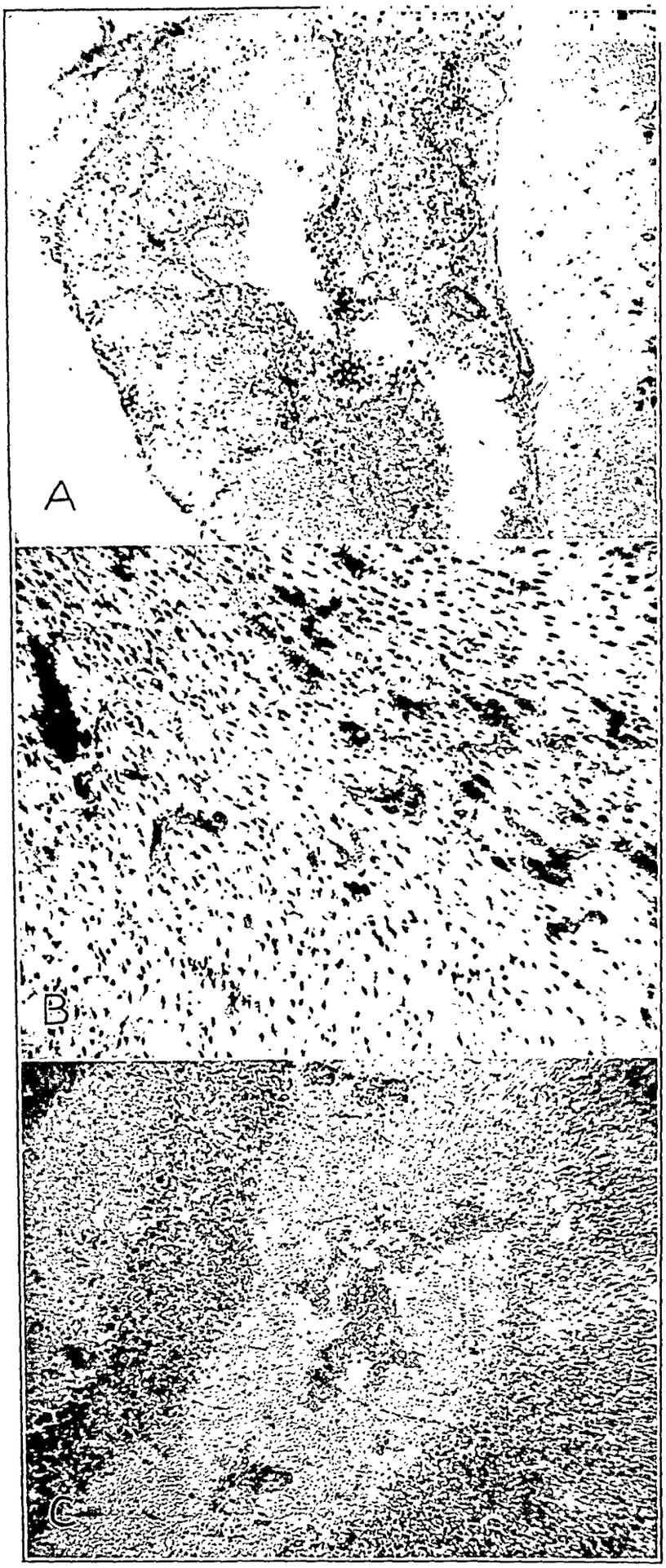


Fig. 9.—*A*, subarachnoid hemorrhage encroaching on the tip of the right frontal lobe. There was no evidence of skull fracture. The animal, rat 41, received ten subconcussive blows at long intervals (moving head struck against stationary object) and was repeatedly made unconscious from the fifth to the tenth blow. After the last blow the rat did not regain consciousness and died twenty-four hours later. Starting at the eighth blow it showed persisting slight psychomotor disorders. Ocular 4; objective 10.

B, recent hemorrhagic extravasations in the cortex of the occipital region of rat 27, which had received fifteen subconcussive blows at long intervals and was repeatedly made unconscious, starting at the sixth blow; it was killed two hours after the last blow. No evidence of fracture of the skull was found. Ocular 4; objective 10.

C, small hemorrhagic effusions in the white matter of the cerebellum. The animal, rat 38, had been made repeatedly unconscious by subconcussive blows at long intervals (moving head struck against stationary object) and was killed twenty-four hours after the last blow. The skull was intact. Ocular 4; objective 10.

gastric mucosa in this animal. In another animal, rat 47 (fig. 7), which had a history like that of the preceding animal but died in twenty-four hours, of acute generalized pulmonary edema, two punctate hemorrhages were noted in the right temporal lobe. In a third animal, rat 92 (fig. 8), which was unconscious for about one hour after receiving nine blows in close succession and died seven days later, extensive subarachnoid hemorrhages were seen in the temporoparietal region of both hemispheres, in the cerebellum and in the brain stem, with slight hemorrhagic involvement of the cerebral cortex. A fourth animal, rat 94 (fig. 8), made unconscious by fifteen blows in close succession, revealed at its death, four days later, a thin layer of clotted blood between the cerebellum and the meninges.

Hemorrhagic changes, of less extent, were seen in 3 other rats which had repeatedly been made unconscious by several blows delivered at intervals of two to six days (table 3). In 1 animal, rat 41 (fig. 9 *A*), the significant changes consisted of a subarachnoid hemorrhage encroaching on the olfactory lobes and the tips of the frontal lobes; in another, rat 38 (fig. 9 *C*), small hemorrhagic effusions were seen deeply embedded in the cerebellar white matter. In a third, rat 27 (fig. 9 *B*), several collections of recently extravasated red blood cells were seen in the cortex of the cerebral hemispheres.

Microscopic Observations.—The hemorrhages in these animals certainly constituted the most obvious evidence of lesion, but they did not indicate that the damage had been restricted to these areas; in fact, other parts, apparently undamaged, of the same injured brains, when examined with specific methods, showed evidence of more extensive organic damage, involving, in a disseminated fashion, both nerve cells and nerve fibers. This appeared to be true, also, for other animals, in which, unexpectedly, properly stained sections revealed damage the existence of which could hardly be suspected on gross inspection of the brains, and even on examination of the sections routinely stained with hematoxylin and eosin.

In the rats which had received the repeated blows in close succession the evidence of neuronal damage was found to be at the same stage in the different areas of the brain of the same animal (figs. 10, 11, 12 and 14). Progressive stages of a fundamentally similar neuronal injury were seen, on the contrary, in different areas of the same brain in the animals submitted to the trauma at longer intervals, suggesting cumulation of damage with each successive blow (fig. 13).

Of these changes of microscopic dimensions, the most apparent was rarefaction of the nerve cells of the cerebral cortex. This rarefaction was not diffuse, as areas showing normal stratification and density of nerve cells alternated with other areas exhibiting obscuring of stratification and diminution of neurons, affecting especially the pyramidal cells. Elsewhere the nerve cells seemed to be undergoing some form of gradual atrophy, with shrinkage of the cell bodies, which stained deeply and showed absence of expansions (aneuritic cells). Other cells exhibited diminished clearness of the cell outlines, with tigrolysis, or glassy cytoplasm, or with huge cytoplasmic vacuoles, which displaced the nucleus to the periphery of the cell body. Around these damaged elements groups of glia cells were noticeable at times.

With corresponding distribution, the apical dendrites appeared thickened, with a somewhat spiral course and at times a definite corkscrew shape. Some of these apical dendrites were poorly impregnated; others were overstained with the reduced silver. Pale and deeply stained segments often alternated in the same fiber. More advanced neurolytic changes were noticeable in other areas of the same brains, in which the situation of the apical dendrites was indicated by only a few fragments and by tail-like rows of disappearing granules. The focal distribution of these changes resulted in an irregular alternation in the same microscopic field of apical dendrites apparently intact and of other dendrites revealing all stages of a progressive neurolytic process.

The same type of focal change was shown by the medullated axons, which in scattered areas displayed varicose swelling and corkscrew twisting, with formation of peculiar loops and spirals. Other fibers revealed evidence of fragmentation, with dustlike granules and balls here and there, mostly free but occasionally still hanging to the ends of the degenerated portions of interrupted fibers.

Changes of corresponding severity were displayed by the myelin sheaths, some of which showed fusiform or ovoid swelling, resulting in a moniliform appearance, which contrasted sharply with the straight linear course of nearby undamaged sheaths; other sheaths appeared to be under incipient reabsorption, with resolution into round, oval or irregularly shaped globules. Disseminated areas of complete demyelination were occasionally seen; and where demyelination and breaking down of axons were still continuing, there was a quantitative increase of microglia cells, with all stages of transformation into rod cells, various bizarre-shaped scavenger cells and,

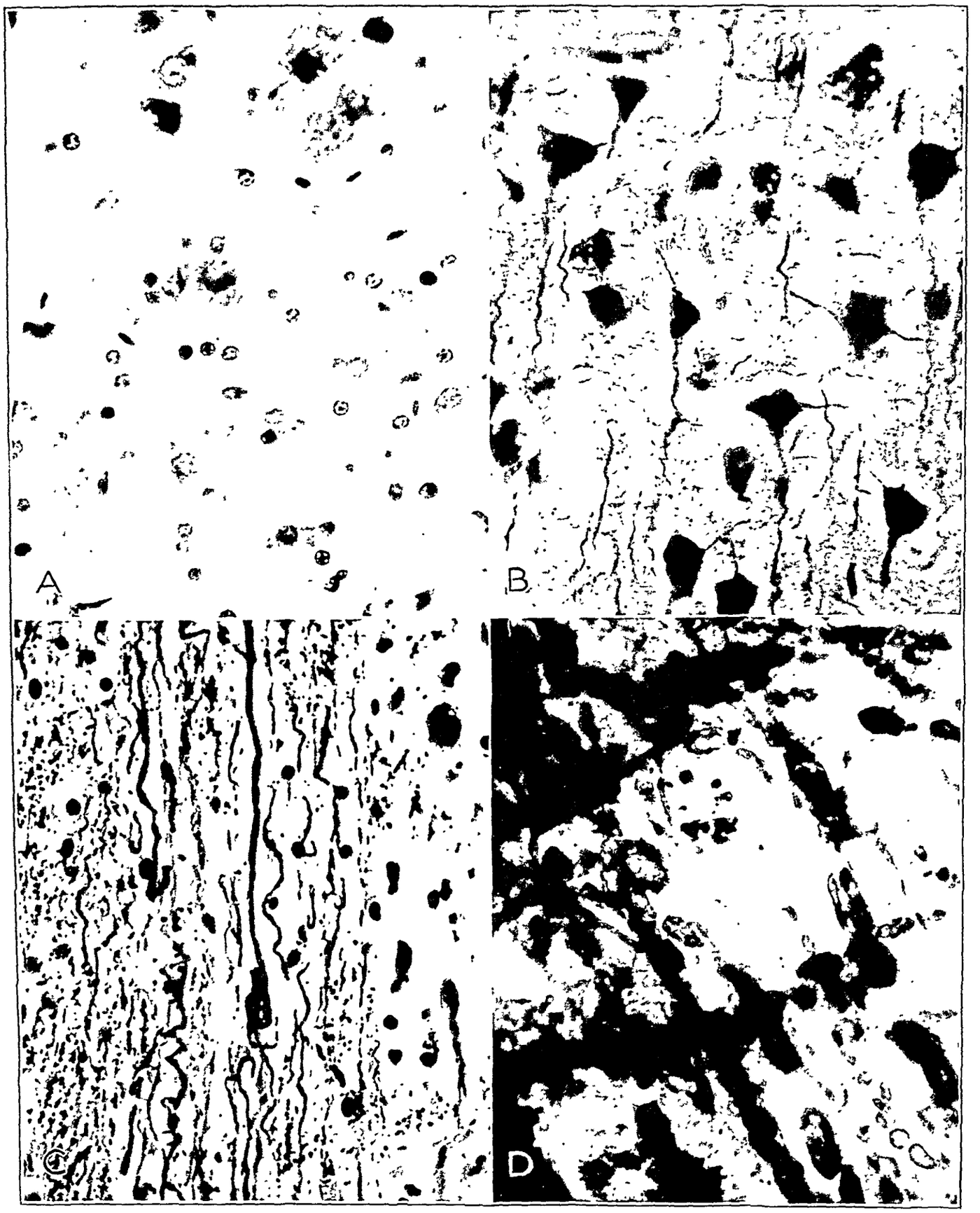


Fig. 10.—*A*, swelling, vacuolation and pericellular edema of nerve cells in the cortex of the frontal lobes of rat 99, which was unconscious for five minutes after receiving eleven subconcussive blows in close succession (moving head struck against stationary object). Three hours later, when the animal was killed, the skull, brain and cerebral involucres were apparently intact. Nissl stain; ocular 6; objective 40.

B, from a section at the same level as that from which *A* was taken, showing thickening, spiroid course and, at times, corkscrew twisting of the apical dendrites. Cajal stain; ocular 6; objective 40.

C, bundle of medullated axons in the right frontothalamic tract of rat 99, showing swelling, twisting, spiroid course and fragmentation of nerve fibers and overstaining nerve fibers with the reduced silver (preservation necrosis). Cajal stain; ocular 4; objective 40.

D, individual myelin sheaths from a section at the same level as that from which *C* was taken, showing moniliform swelling and fragmentation, with reabsorption in areas and resolution into round, oval or irregularly shaped globules. Spielmeyer stain; ocular 6; objective 40.

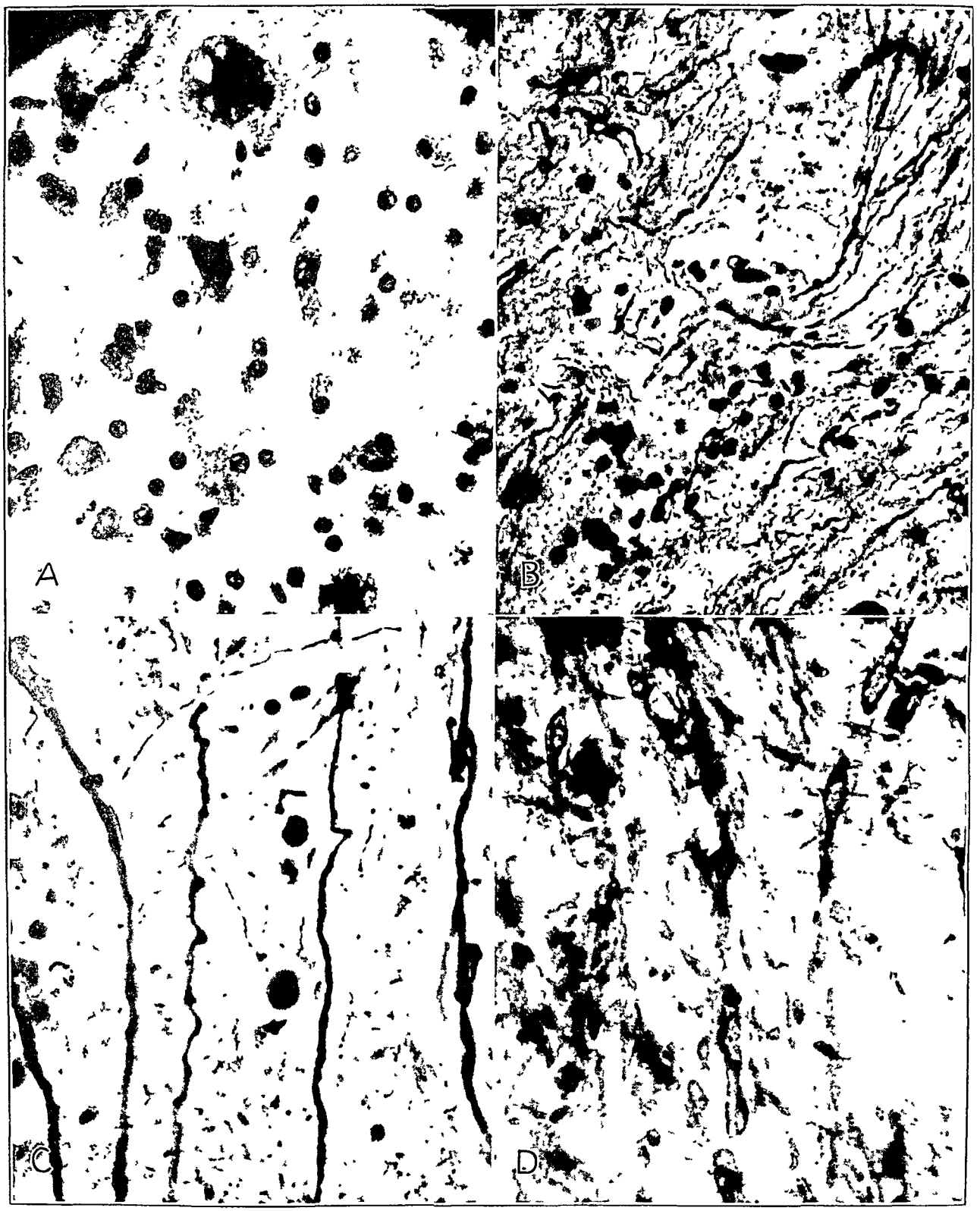


Fig 11.—*A*, from the brain of rat 75, which received the same treatment as rat 99, eleven subconcussive blows in close succession, but with the other mechanism of trauma—moving object striking against the stationary head. At the last blow the animal was unconscious for four minutes, and it was killed three hours later. The Nissl preparation showed tigrolysis and pronounced pericellular edema of cortical nerve cells. Ocular 6; objective 40.

B, a bundle of medullated axons in the floor of the fourth ventricle of rat 75, displaying nerve fibers which are spread apart, fragmented and undergoing incipient granular disintegration. Evidence of mobilization of *microglia cells is already noticeable in the damaged area. Ocular 6; objective 10.*

C, from the field shown in *B*, higher magnification, showing the marked twisting and spreading apart of nerve fibers, with formation of bizarre-shaped loops and spirals. Cajal stain; ocular 6; objective 40.

D, myelin preparation of a section at a corresponding level, showing conspicuous varicose swelling and disintegration of myelin sheaths, with formation of ellipsoids and fat droplets. Spielmeyer stain; ocular 6; objective 40.

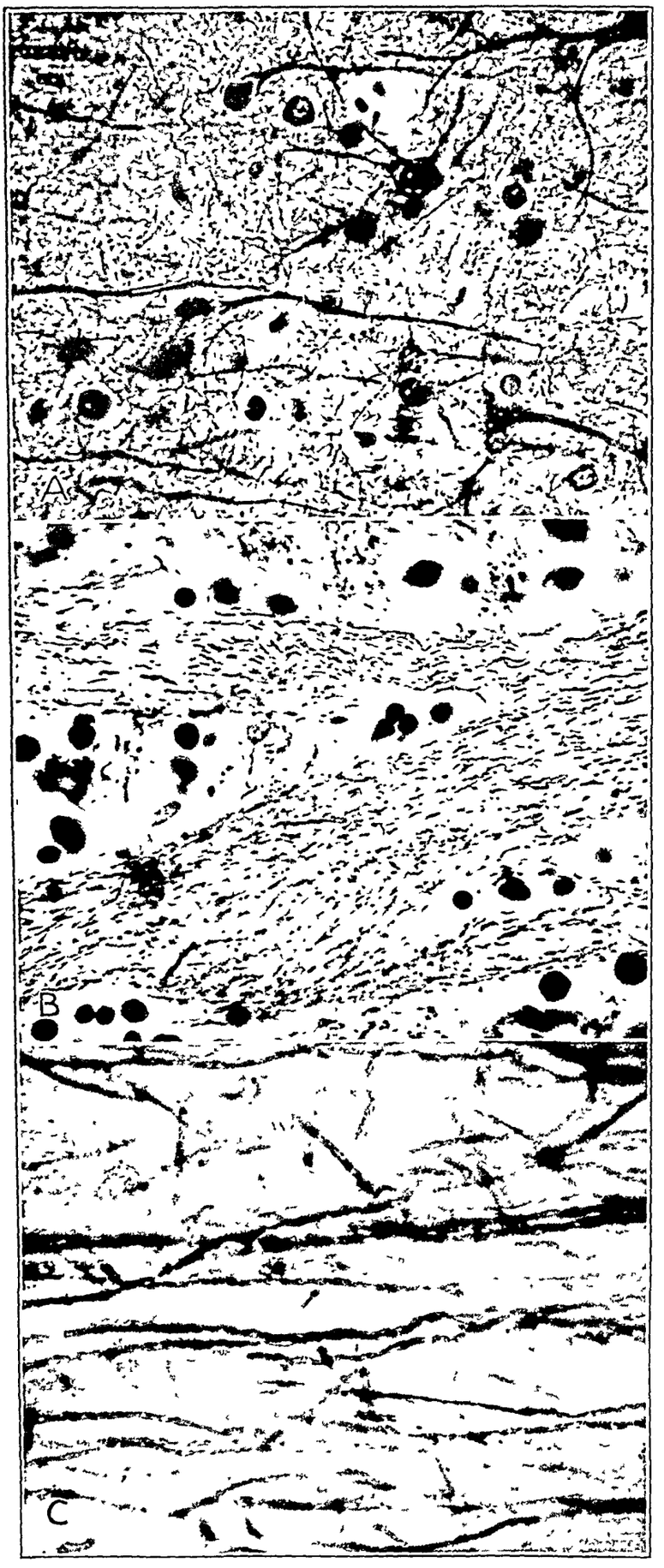


Fig. 12.—From the brain of an animal, rat 101, apparently unaffected by trauma of a severity approximately corresponding to that received by rats 99 and 75—fifteen blows in close succession, with the moving head struck against a stationary object. The rat was killed three hours later. The straight and regular course of the axis-cylinders (*A*, Cajal stain); the compactness of the bundles of nerve fibers, which appear to be homogeneously stained (*B*, Cajal stain), and the linear arrangement and uniform thickening of the myelin sheaths (*C*, Spielmeyer stain) are in sharp contrast to the corresponding damaged structures of rats 99 and 75. Ocular 4; objective 40.

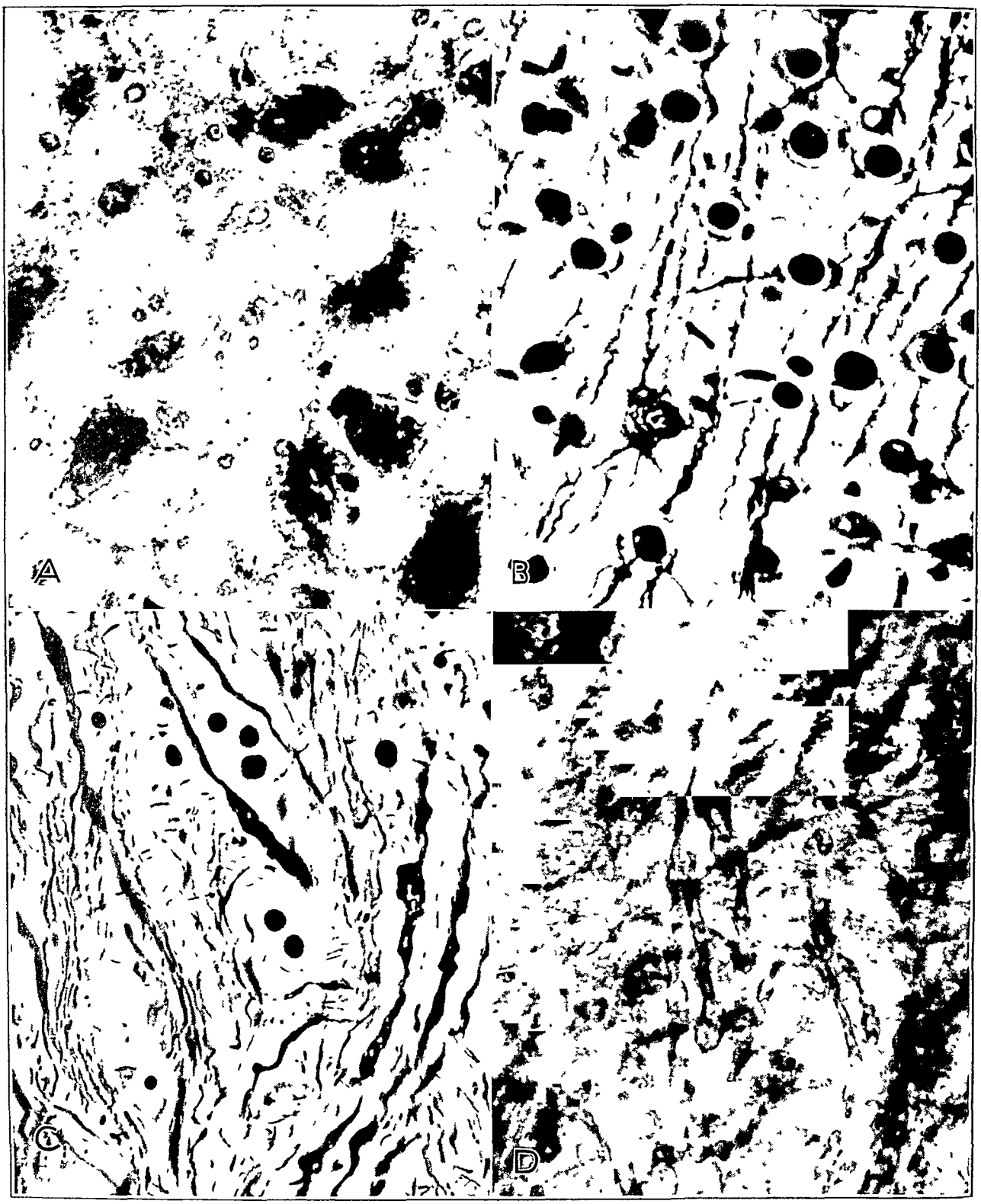


Fig. 13.—*A*, tigrolysis, swelling and pericellular edema of cortical nerve cells, from the brain of an animal, rat 35, which received eight subconcussive blows at long intervals—with the moving head struck against the stationary object—and was made unconscious at the seventh and eighth blows. At death, twenty-four hours later, the skull, brain and cerebral involucres were apparently intact. Nissl stain; ocular 6; objective 40.

B, from a Cajal preparation taken at a level corresponding to that from which *A* was taken, showing absence of expansions of the nerve cells (aneuritic cells), corkscrew twisting and fragmentation of the axons and tail-like rows of disappearing granules. Ocular 6; objective 40.

C, from a section at the level of the pons of rat 35, showing twisting and fragmentation of fibers, with formation of bizarre-shaped loops and spirals. The fusiform swelling at the ends of the degenerated portions of the interrupted fibers is clearly seen. Cajal stain; ocular 6; objective 40.

D, myelin swelling at the ends of the degenerated portions of fragmented fibers, from a section obtained at a level corresponding to that from which *C* was taken and stained for myelin by the Spielmeyer method. Ocular 4; objective 40.

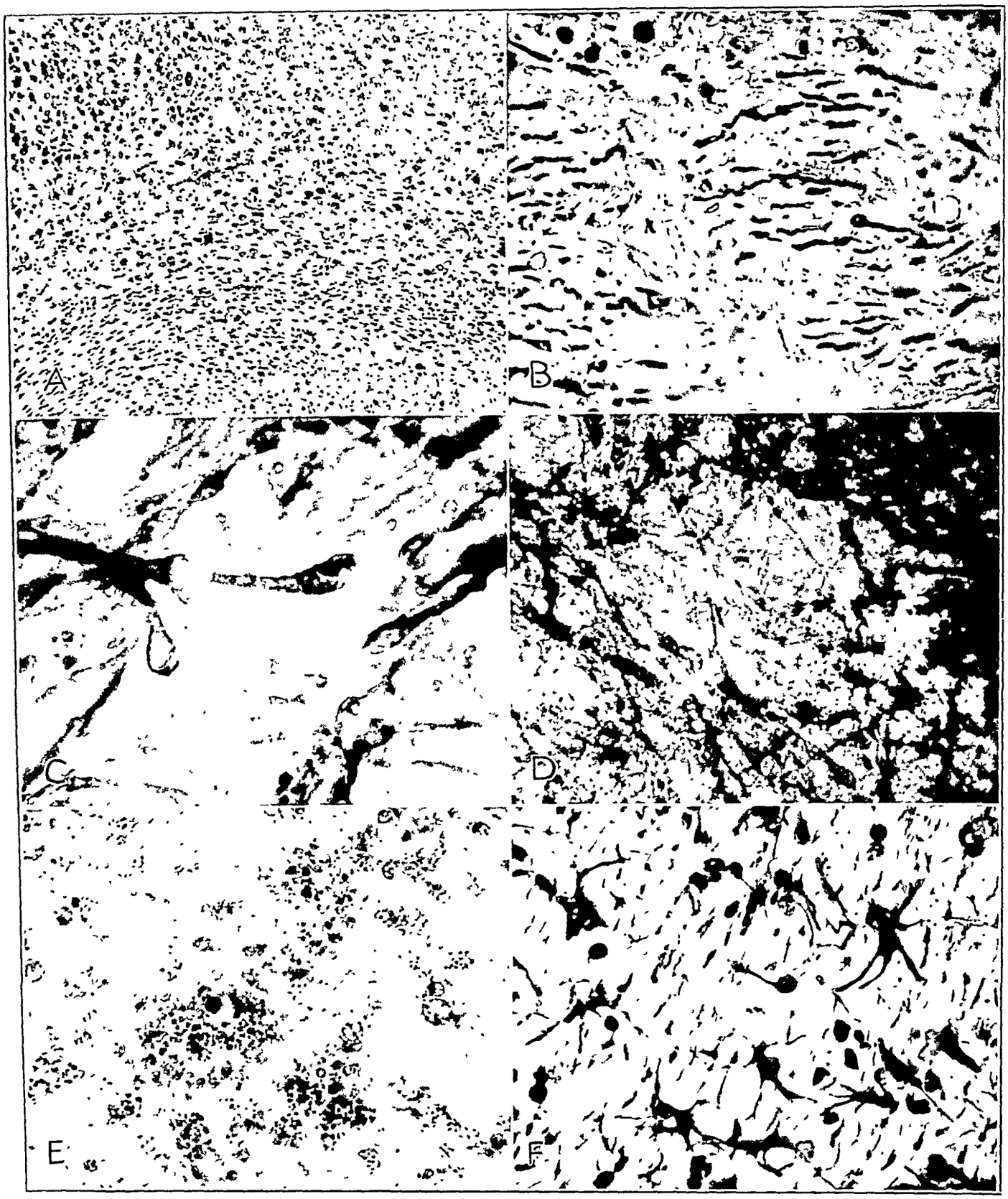


Fig. 14 (rat 54).—*A*, obscuring of stratification, shrinkage and pyknosis of nerve cells of the cortex (occipital lobe) in a rat which after the trauma had shown marked psychomotor disorders (figs. 5 and 6). The animal was unconscious for a few seconds after receiving fourteen subconcussive blows in close succession on the stationary head and died twenty-nine days later. The skull, brain and meninges did not reveal any abnormalities post mortem. Nissl stain; ocular 4; objective 10.

B, remnants of medullated axons, showing fusiform swelling and typical bulbs of retraction at the ends of degenerated portions of fragmented fibers. Cajal stain; ocular 6; objective 10.

C, myelin swelling, resulting in clublike formations at the ends of fragmented fibers, from a section taken at a level corresponding to that of *B*. Spielmeyer stain; ocular 6; objective 40.

D, from another area of the brain of the same rat, showing extensive reabsorption of myelin and resolution into round, oval or irregularly shaped globules. Spielmeyer stain; ocular 4; objective 40.

E, fat globules, for the most part free and to a less extent contained within compound granular corpuscles in a preparation taken at approximately the same level as that shown in *C* and stained with oil red O. Ocular 4; objective 40.

F, hyperplasia of astrocytes, not accompanied with any appreciable increase of glia fibers, in a damaged area of the perithalamic region of the brain of the same rat. At the center of the picture a ball-like formation hanging at the end of a fragment of nerve fiber is recognizable. Cajal stain; ocular 6; objective 40.

ultimately, into round, vacuolated cells, with small dark nuclei and cytoplasm loaded with fat globules. Evidence of glia reaction in the parts that were damaged was encountered at times, but the hyperplasia of the astrocytes was not accompanied, in most cases, with any appreciable increase of glial fibers.

COMMENT AND CONCLUSIONS

Rats recovering from a temporary period of unconsciousness, varying from ten seconds to fifteen minutes, following a single blunt impact on the head which had left the skull and brain apparently intact on gross inspection, consistently revealed widespread microscopic evidence of neuronal injury, affecting in a disseminated fashion both nerve cells and nerve fibers.

These findings suggest that concussion may be due to neuronal injury detectable with present histologic methods. Nothing more definite can be claimed, however, since one cannot rule out the possibility that these changes are secondary to other factors primarily involved in the phenomenon of concussion.

Evidence of neuronal damage was noticed as early as one to two hours after the trauma, and in a few animals the lesions were seen to persist as long as two months after the trauma. Of the residual changes, the presence of free balls in areas showing obliteration of neurons was the most apparent. This is in agreement with the observations of Penfield,[18] and with those of Rand and Courville,[10] who noted these alterations in traumatized brains months or years after the accident.

The part that these residual changes might play in the development and in the persistence of late-appearing functional disorders necessarily depends on the location and extent of the neurons involved and on the possibility of a redistribution of impulses through undamaged pathways.

In an attempt to analyze the possible factors which could account for these neuronal changes, it becomes apparent that nerve cells and nerve fibers may be affected in a number of ways after mechanical violence to the head. Cerebral edema, cortical and subcortical hemorrhage, so much emphasized by other investigators in interpreting changes in neurons, not only in contused areas but in remote and otherwise undamaged portions of the brain (Greenfield,[14] Schwartz and Fink [13]), were rarely encountered in my material. In the light of old and recent observations, the influence of "shear strains" must be considered. Ramón y Cajal [19] emphasized the susceptibility of the neurons of young experimental animals to the effects of minimal amounts of trauma. Rand and Courville,[10] in human material, suggested the possibility of rupture of nerve fibers as the result of the "shock of the injury." Greenfield [14] pointed out the facility with which the single anatomic units of the brain and their connecting pathways, as well as the whole brain in relation to the skull, may be distorted, stretched or torn whenever the brain is made to alter its shape. Forces connected with acceleration, according to Denny-Brown and Russell,[4] and forces connected with rotation of the brain within the skull, according to Holbourn,[20] are likely to produce an amount of cerebral damage greater than that produced when distortion of the skull is the principal effect of the impact.

Concussive effects following a single blow were obtained consistently in the present experiments, a trauma of the same momentum being used with each mechanism, one of which involved forces of acceleration mainly and the other forces of distortion, and neuronal damage of approximately the same type, magnitude and depth was observed in all animals. As my experimental procedures are different from those used by Holbourn [20] and by Denny-Brown and Russell,[4] the results of these authors cannot be compared directly with mine in this respect.

On the other hand, the results of my experiments are in agreement with the conclusions reached by Denny-Brown and Russell in regard to a "threshold value" in the mechanism of concussion, as concussive effects after a single blow could be obtained with consistent frequency once the strength of the trauma had reached a certain level, as determined in the preliminary experiments. This may indicate that a certain basic amount of damage is necessary for the production of the phenomenon of concussion.

If this concept is true, the appearance of ill effects as a result of repeated trauma of minimal intensity might be explained on the basis of cumulated neuronal damage, until the "threshold value" is reached and functional disorders become apparent. Evidence in support of this concept was clearly found in my material, as rats

18. Penfield, W.: Cerebral Cortex in Man: Cerebral Cortex and Consciousness (Harvey Lecture), Arch. Neurol. & Psychiat. **40**:417 (Sept.) 1938.

19. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, translated by R. M. May, London, Oxford University Press, 1928, vol. 2.

20. Holbourn, A. H. S.: Mechanics of Head Injuries, Lancet **2**:438 (Oct. 9) 1943.

submitted to repeated blunt impacts on the head the strength of each of which alone was not sufficient to harm the animal, after a certain number of blows began to reveal ill effects, as shown by unconsciousness, with or without recovery, and at times by persisting functional disorders or by delayed death.

When the repeated subconcussive blows were delivered in a short period, there was a somewhat higher incidence of ill effects than when the trauma was delivered at longer intervals. An explanation of this might be found in the recovery of reversible lesions and in the redistribution of impulses through undamaged nerve pathways in the longer intervals between the blows.

In the great majority of animals there was a certain correspondence between the response to the repeated trauma during life and the amount and extent of cerebral damage, as the latter appeared to be minimal in the animals clinically unaffected and became progressively more severe in the animals which were made repeatedly unconscious or manifested persisting functional disorders as the result of the repeated trauma. In these animals, also, no remarkable differences were noticed in the apparent effects under the two mechanisms of trauma.

Among the postmortem changes, punctate hemorrhages or other types of hemorrhagic change were extremely rare in this material. I am unable therefore to confirm the observation of Shaller, Tamaki and Newman [3] of an apparent increase in vulnerability of the cerebral vessels induced by the application of repeated blows. Evidence of neurolytic changes, accompanied by loss of myelin and, in the later stages, by glial proliferation, was, on the contrary, consistently encountered in my animals.

Assuming that the normal function of the brain is dependent on two factors—the initiation of impulses within the nerve cells and their transmission through the complicated network of nerve fibers—my results point strongly to the possibility of permanent functional disorders, such as those seen in some of the animals, following repeated blows on the head apparently of moderate intensity, the disorders being due not only to a deleterious effect on the nerve cells but to the interruption of nerve impulses consequent to the changes in the nerve fibers.

SUMMARY

Rats submitted to repeated blunt impacts on the head the strength of each of which alone was not sufficient to harm the animal (subconcussive trauma) began to reveal ill effects after a certain number of blows, as shown by unconsciousness, with or without recovery, at times by other, persisting functional disorders and later even by death. When the repeated subconcussive blows were delivered in a short period—one impact after another, one minute apart—there was a somewhat higher incidence of ill effects than when the trauma was delivered at longer intervals—from two to six days apart. No remarkable differences were noticed in the effects when, with a trauma of the same strength, the head in rapidly accelerated motion was made to strike a stationary object and when a moving object was made to strike the fixed head of the animal. In the great majority of animals there was a certain correspondence between the response to the repeated trauma during life and the amount and extent of cerebral damage. Among the postmortem changes, hemorrhage or any other type of change detectable on gross inspection was extremely rare. On the contrary, widespread evidence of neuronal injury, affecting in a disseminated fashion both nerve cells and nerve fibers, accompanied with loss of myelin and, in the later stages, with glial proliferation, was a consistent microscopic observation.

A neuronal injury identical in type was found in collateral experiments in animals recovering from a temporary period of unconsciousness following a single blow on the head which had left the skull and brain grossly intact. Microscopic evidence of neuronal damage was noticed in these animals as early as one to two hours after the trauma, and in a few instances the lesions were seen to persist as late as two months after the trauma. These observations suggest that concussion may be due to neuronal injury detectable with the present histologic methods. With the production of concussion by a single blow, no pronounced differences were noted in the effects when the impact was delivered on the stationary head and when it was delivered on the head in rapidly accelerated motion, with a trauma of the same momentum.

NOTE: This paper was already in course of publication when two important experimental studies on head trauma came to my attention.

In one, by Gurdjian and Webster,[21] it is concluded:

> Higher velocities were required to produce [in dogs] pathophysiologic effects under the circumstances of the

21. Gurdjian, E. S., and Webster, J. E.: Experimental Head Injury with Special Reference to the Mechanical Factors in Acute Trauma, Surg., Gynec. & Obst. **76**:623 (May) 1943.

nonfixed head than the fixed head. . . . However, a greater degree of mass movements of the brain may occur under conditions of a nonfixed head.

In the other, Windle, Groat and Fox [22] found definite neurologic changes accompanied by a variable amount of swelling of the sheaths of the nerve fibers in guinea pigs struck on the head once or repeatedly. In agreement with my own observations, the amount of damage they found was proportionate to the strength and number of blows; and in a limited number of animals, while a single subconcussive blow was ineffective, two subconcussive blows produced as much damage as a single light concussive blow. Hence their conclusion that "these histological changes do serve as visible indicators of the ravages of a concussional force."

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

Medfield State Hospital.

STUDIES OF THE SENSATION OF VIBRATION

III. EVIDENCE FOR CORTICAL AREAS IN INHIBITION AND MEDIATION OF TICKLE

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In experiments on the functions of the frontal lobe, we performed a number of different examinations,[1] among which was the determination of the vibratory threshold. Of 3 patients with lesions of the right frontal lobe who were examined, the results for 1 lead us to conclude that two areas are present in the cortex in the mediation of tickle: One area is the primary tickle center, and the other area inhibits this center. This peculiarity of the functions of the cortical areas involved in the perception of tickle, and the belief that tickle is not a pure sensation but is produced by a combination of sensory qualities, such as touch and pain,[2] with the consequent rare examination of the patient with neurologic lesions for tickle, largely account for the fact that the areas for tickle have not been discovered before.

REPORT OF A CASE

An American-born woman, predominantly right handed, was operated on twice for a tumor of the right frontal lobe. On Jan. 18, 1940, at the age of 37, she was first admitted to the hospital, with a history of convulsions, dizziness, vomiting, diminution of vision and slowing of mental processes. These symptoms had increased in severity for six months preceding her admission to the hospital. Examination showed bilateral loss of vision and slight paresis of the muscles of the left side of the face, the right palpebral fissure being wider than the left. A ventriculogram confirmed the diagnosis of tumor of the right frontal lobe. Operation was performed on January 24, and a cystic tumor (later determined to be a protoplasmic astrocytoma) was removed. The mass of tissue extirpated weighed 106 Gm. The area of the tissue removed in this patient (*6*) is shown diagrammatically in figure 1. This figure also shows the areas of the extirpated tissue in 2 other patients (*1* and *4*) with lesions of the right frontal lobe whose vibratory thresholds were determined, and a diagram indicating the overlapping of the areas of the lesions of the last 2 patients with the area of extirpation in the first patient.

The patient's recovery was uneventful, and no neurologic dysfunction was present except the loss of vision. She was able to perceive bright lights and movement but could not perceive any details. Her postoperative intelligence quotient for the verbal part of the Wechsler-Bellevue test was 116. She began to study Braille and made other adequate adjustments to her environment. The only personality characteristics which could be associated with the lesion was a mild degree of facetiousness and irritability.

Twenty months after the operation a relapse occurred. The patient had numerous convulsions, involving largely the left side of the face and the left arm, and headaches in the area of the right temporal lobe. A second operation was performed on Dec. 12, 1941, at which time 90 Gm. of tissue was removed. A photograph of the area of the lesion produced by the two operations is shown in figure 2. The postoperative recovery of the patient was at first uneventful. The neurologic symptoms consisted of some motor paralysis, decrease in the sensation of touch and astereognosis involving in each case the left side of the body. On Jan. 26, 1942 the patient became mentally confused. Rage reactions occurred periodically. She had visual hallucinations and became incoherent and extremely facetious. These periods were interspersed with periods of lucid behavior and lethargy. On March 20, 1942 she died, of circulatory failure with pneumonia and encephalitis.

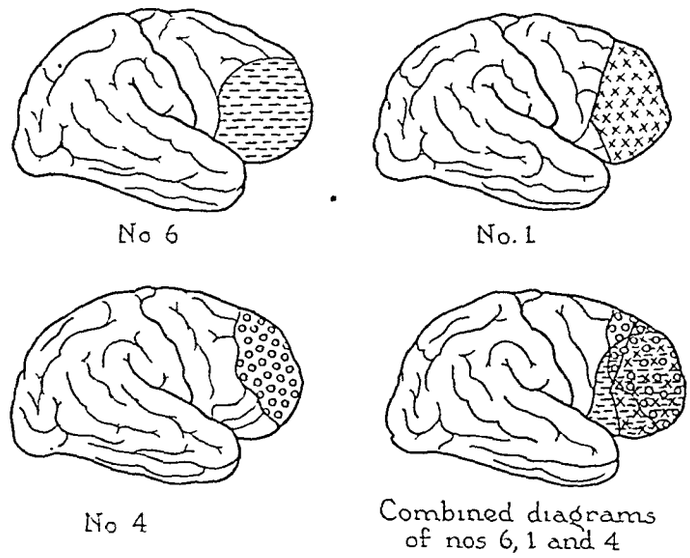

Fig. 1.—Diagrams showing the amount of tissue extirpated after the first operation on patient 6, who displayed the abnormal tickle response, and the lesions of 2 control patients, 1 and 4. The composite diagram shows that the lesions of the controls did not overlap the lesion of patient 6 in the inferior and posterior areas.

From the Department of Nervous and Mental Diseases and the Department of Surgery, Northwestern University Medical School.

1. Yacorzynski, G. K., and Davis, L.: Modification of Perceptual Responses in Patients with Unilateral Lesions of the Frontal Lobes, Tr. Am. Neurol. A. **68**: 122, 1942; An Experimental Study of the Functions of the Frontal Lobes in Man, Psychosom. Med. **7**:97, 1945.

2. Since, to the best evidence, tickle is not a simple sensation but is produced by a combination of sensory qualities, it is only logical that this response be classified as a perception rather than a sensation.

DETERMINATION OF VIBRATORY THRESHOLDS

The vibratory thresholds were determined by an apparatus which has already been described [3] and which allows measurement of the thresholds through a large range of sinusoidal frequencies, with precise determination of the amplitude of the vibrating pointer when placed directly against the skin. After the first operation attempts were made to measure the vibratory thresholds of the patient at the different frequencies, with the result that, rather than experiencing the sensation of vibration, she usually perceived tickle, which was at times so excruciating that she would break out into hilarious laughter. The finger tips, the ventral and dorsal surfaces of the hands and arms and the sides of the face were examined. The sensation of tickle was more pronounced on the left side of the body than on the right side. Thus, on the ventral surface of the left hand she perceived a sensation of tickle at all of the frequencies which could be tested with the apparatus (from 50 to 500 double vibrations), whereas on the right side she perceived the vibrations at all of the frequencies except at 50 double vibrations, at which she perceived tickle. Intermittently, on the areas of the right side which were tested she would at times fail to perceive tickle at some frequencies,

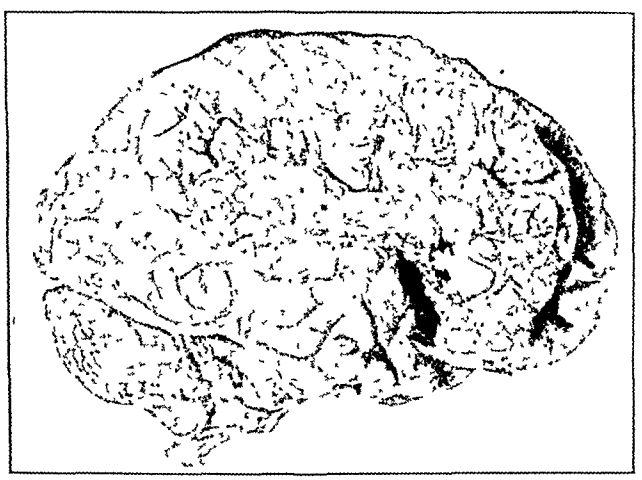

Fig. 2—Lateral view of the brain of patient 6.

although this occurred very seldom when the left side was stimulated. She reported that she had become more ticklish after the operation but that prior to the operation she had not considered herself abnormally ticklish. To substantiate this statement, she recounted the following incidents: While at the hospital after the first operation the nurse was greatly annoyed by her laughter when she was given a bath and a massage. The patient stated, "I felt as if the nurse was hitting every ticklish spot I had." When she returned home, her sister discovered that all she had to do to win an argument was to tickle the patient.

These results were unusual in that normal subjects studied by us seldom report a sensation of tickle when the vibrating pointer is placed against the skin, and that 2 other patients with cerebral lesions of the right frontal lobe experienced only the normal vibrations and gave threshold readings characteristic of normal subjects. Being cognizant, however, that there is a wide difference between persons in susceptibility to tickle, and that tickle is subject to much learning, we did not place great emphasis on the results until the second operation. At that time the perception of tickle to the vibratory stimulus disappeared completely on both sides of the body, and, although the patient was examined a number of times, no tickle response to the vibratory stimulus could be elicited. The patient also reported that she was no longer ticklish.

INTERPRETATION

These results can be interpreted by postulating that an area exists in the brain which is involved in the mediation of the perception of tickle and that a second area is present which inhibits the primary tickle area. When the inhibitory area is destroyed, a release of the inhibition takes place, so that tickle becomes more pronounced. Presumably, that is what occurred after the first operation. The second operation, according to this conception, would have destroyed the primary tickle area.

In advancing the conception that an area is present in the cortex which functions to inhibit another cortical area, we are not postulating a completely novel mechanism. Dusser de Barenne, Garol and McCulloch,[4] Fulton and Kennard [5] and Hines [6] have shown that areas are present in the frontal lobes which function to inhibit the motor cortex. Two areas, 4 S and 8 S, which inhibit area 4 have been identified in the monkey. The release phenomenon of the tickle reaction simulates the release of the motor responses in other ways. We found that although tickle was obtained predominantly when the contralateral side of the body was stimulated, the response in general had a bilateral distribution and showed no evidence of topographic localization. Hines [6] has shown that removal of the "strip" area (area 4 S) on one side produced a generalized bilateral motor release, although contralateral symptoms were dominant.

The area involved in the inhibition of tickle can be estimated by comparing the size of the lesion of the patient who displayed the release phenomenon with the amount of destruction of 2 other patients with lesions of the right frontal

3. Yacorzynski, G. K., and Brown, M.: Studies of the Sensation of Vibration: I. Variability of the Vibratory Threshold as a Function of Amplitude and Frequency of Mechanical Vibration, J. Exper. Psychol. **28**:509, 1941. Brown, M., and Yacorzynski, G. K.: Studies of the Sensation of Vibration: II. Vibration Sensibility in the Face Following Retrogasserian Neurectomy, Arch. Neurol. & Psychiat. **47**:813 (May) 1942.

4. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Physiological Neuronography of the Cortico-Striatal Connections, A. Research Nerv. & Ment. Dis., Proc. **21**:246, 1942.

5. Fulton, J. F., and Kennard, M. A.: Study of Flaccid and Spastic Paralyses Produced by Lesions of the Cerebral Cortex in Primates, A. Research Nerv. & Ment. Dis., Proc. **13**:158, 1934.

6. Hines, M.: The "Motor" Cortex, Bull. Johns Hopkins Hosp. **60**:313, 1937.

lobes who did not show an abnormal change in perception of tickle. A diagram showing such a comparison is included in figure 1. It is seen that the lesions of the controls do not overlap the lesions of the patient showing the release of tickle in Brodmann's areas 44 and 45, the dorsal parts of areas 11 and 47 and the lower anterior part of area 9. Presumably, therefore, the center inhibiting tickle is located in these areas.

The determination of the center involved in the mediation of tickle presents more difficulty, since any part of the cerebrum destroyed by the second operation may be the area concerned. This lesion includes the Brodmann areas 41, 42, 43 and 52, the lower part of area 6, the lower tip of area 3, the anterior and inferior parts of area 40 and the superior portion of area 22. If tickle involves a perceptual response rather than a pure sensation, as the evidence on this sense seems to indicate, one would expect that its center would not be found in the postcentral gyrus involved in the mediation of the primary sensations, but would probably be posterior to this area, as is, for example, the case with stereognosis. This would involve the region which was destroyed on the inferior aspect of the parietal lobe, or area 40. We should not exclude, however, the possibility that involvement of the basal ganglia of the telencephalon following the second operation may have been responsible for the diminution of tickle, since a coronal section at the tips of the temporal lobes showed some traumatic and degenerated changes in these areas. Bucy [7] stated the opinion that areas 4 S and 8 S mediate the inhibitory impulses to the motor cortex through the basal ganglia. However, even should the impulses of the inhibitory tickle area reach the primary tickle area through neural connections with the basal ganglia, there is little reason to suppose that the interruption of such pathways would in any way produce a diminution of the release phenomenon following the destruction of the inhibitory center, unless, of course, the mechanism involved in the perception of tickle is entirely different from that existing in the motor field.

7. Bucy, P. C.: The Neural Mechanisms of Athetosis and Tremor, J. Neuropath. & Exper. Neurol. **1**: 224, 1942.

SUMMARY

Two operations were performed on the right cerebral hemisphere of a patient. After the first operation a vibrating pointer placed against various parts of the body elicited an intense perception of tickle. The hyperesthesia showed no topographic localization and was bilateral, although it was more pronounced when the contralateral side of the body was stimulated. After the second operation the response of tickle to a vibrating stimulus disappeared. In normal subjects and in 2 subjects with lesions of the right frontal lobe a vibrating stimulus applied against the skin seldom produced a sensation of tickle.

These results indicate that in the mediation of tickle two centers are involved. One center is primarily involved in the mediation of tickle, and the other inhibits the tickle center. According to this conception, the inhibitory center was destroyed after the first operation, producing the release phenomenon, and the tickle center was destroyed after the second operation, eliminating the abnormal tickle response. A mechanism similar to the one described here has been found for the motor responses. The inhibitory center for tickle appears to be located in the inferior and posterior portions of the frontal lobe and the tickle center probably in the inferior part of the parietal lobe.

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PRETRAUMATIC PERSONALITY AND PSYCHIATRIC SEQUELAE OF HEAD INJURY

I. CATEGORICAL PRETRAUMATIC PERSONALITY STATUS CORRELATED WITH GENERAL PSYCHIATRIC REACTION TO HEAD INJURY BASED ON ANALYSIS OF TWO HUNDRED CASES

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Psychiatric symptoms are common among the sequelae of head injury.[1] These symptoms may vary in quantity, intensity and duration from case to case. At one extreme may be merely increased irritability. At the other extreme may be a fully developed neurotic syndrome. In association with these symptoms are often prolonged invalidism and delay in resumption of occupation, or, in military life, delay in return to active duty.[3]

Various opinions have been offered as to the causation of these post-traumatic psychiatric syndromes. The subject has been ably reviewed by Strauss and Savitzky[4] and by Schilder.[5] The belief was expressed that the psychiatric sequelae of head injury are due mainly to anatomic and physiologic changes in the brain,[6] that they result from an interest in gaining compensation,[7] that they are largely ascribable to pretraumatic abnormalities of the personality[8] and that there is high correlation with various associated factors, such as occupational, litigational and marital stresses.[9]

This paper is the report of an investigation into the possible relation between the over-all pretraumatic personality and the psychologic sequelae of head injury.

MATERIAL

This inquiry was undertaken as part of a comprehensive study of civilian head injury conducted at the Boston City Hospital from July 1942 to October 1944 by a group under the direction of Dr. Denny-Brown, consisting of neurologists, psychiatrists, a psychometrist, an electroencephalographer, a social worker and a resident physician who had been trained in neurology and psychiatry.

Two hundred subjects were selected for intensive study out of 430 patients who were initially studied on their admission to the hospital. These 200 patients were selected by exclusion of persons in the following categories: persons under 15 and over 55 years of age, vagrants, irresponsible alcoholic addicts, chronically unemployed persons and a few others on whom follow-up study was unobtainable. The groups comprised 125 males and 75 females. The occupational distribution was as follows: skilled or semiskilled workers, 48 per cent; domestics or housewives, 19 per cent; students, 10 per cent; civil employees (firemen, police officers), 6 per cent; unskilled laborers, 5 per cent; unclassified persons, 12 per cent. All patients had been followed until their symptoms had disappeared and they had returned to full employment or for a period of at least six months from the time of discharge from the hospital.

All patients had been admitted to the hospital promptly after injury. In general they had suffered "closed" head injuries. Only 6 patients had compound fractures. The patients varied in their neurologic and psychologic manifestations. The injury of 85 patients would in general neurologic practice be diagnosed as

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Part II (in preparation) deals with multiple, specific personality factors present both before and after head injury.

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The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College.

1. (*a*) Denny-Brown, D.: Disability Arising from Closed Head Injury, J. A. M. A. **127**:429-436 (Feb. 24) 1945. (*b*) Symonds, C. P., and Russell, W. R.: Accidental Head Injuries: Prognosis in Service Patients, Lancet **1**:7-10, 1943.

2. Footnote deleted.

3. Lewis, A., in Discussion of Differential Diagnosis and Treatment of Postcontusional States, Proc. Roy. Soc. Med. **35**:607-614, 1942.

4. Strauss, I., and Savitsky, N.: Head Injury: Neurologic and Psychiatric Aspects, Arch. Neurol. & Psychiat. **31**:893-955 (May) 1934.

5. Schilder, P.: Neuroses Following Head and Brain Injuries, in Brock, S.: Injuries of Skull, Brain and Spinal Cord, Baltimore, William Wood & Company, 1940.

6. Oppenheim, H.: Die traumatischen Neurose, Berlin, A. Hirschwald, 1889, p. 146.

7. Schaller, W. F.: After-Effects of Head Injury, J. A. M. A. **113**:1779-1785 (Nov. 11) 1939.

8. (*a*) Symonds, C. P.: Mental Disorder Following Head Injury, Proc. Roy. Soc. Med. **30**:1081-1094, 1937. (*b*) Symonds and Russell.[1b] (*c*) Lewis.[3]

9. Adler, A.: Mental Symptoms Following Head Injury: A Statistical Analysis of Two Hundred Cases, Arch. Neurol. & Psychiat. **53**:34-43 (Jan.) 1945.

"concussion," the degree of severity depending on the length of coma. Twelve patients had no initial traumatic impairment of consciousness other than a momentary daze. In all, 34 had fractures of the skull. The cerebrospinal fluid of 46 patients was blood tinged. Thirty-two patients presented abnormal neurologic signs. In 14 patients focal injury to the brain was indicated by the presence of cranial nerve palsies, dysphagia and/or convulsive seizures. Twenty patients had no history of coma following injury; 92 were in coma or semicoma for less than ten minutes; 42, from ten to thirty minutes; 20, from thirty to sixty minutes; 17, from one to six hours; 4, from six to twenty-four hours, and 4 over twenty-four hours. Eighteen patients were not disoriented; 155 patients showed disorientation for variable periods, up to twelve hours; 4 patients, from twelve to twenty-four hours; 12 patients, from one to seven days, and 11 patients over a week.

METHOD

Evaluation of the pretraumatic personality of each patient was based on a history of the personality. In the present state of psychiatry there is no more dependable method of gaining insight into the nature of a personality than through a scrutiny of past performances and experiences in their special settings. No personality test, such as the Rorschach or the Minnesota test, can be depended on to give an evaluation of a patient's personality before injury to the head when the test is given after the injury. Thus, chief reliance was placed on the psychiatric history.

Uniformity of examination was attained by having each patient in the series of 200 examined not only by one of the two psychiatrists in the group but by all the other members of the project staff, including, in most cases, the other psychiatrist. There was general staff discussion of the psychiatric aspects of each patient's case. In addition, each psychiatrist followed a uniform scheme of examination. Not only was the history taken from the patient himself, but the data were checked and supplemented by interviews with relatives, friends, employers and others who might be able to provide information about the patient's behavior. Investigations by a social worker were of particular assistance. At subsequent interviews with the patient the data were rechecked.

As a result of such an investigation, each patient was given a categorical classification of his personality under one of the following headings:

Normal personality
Psychopathic personality
Neurotic personality
Personality variant
Normal personality except for general nervousness
Mental deficiency
Neurotic traits in childhood
Behavior problem (childhood and youth)
Psychotic behavior
Pretraumatic personality unknown

It is recognized that no categorical classification can do justice to the complexity of a personality and that widely dissimilar personalities may be found in the same diagnostic group. Nor do I argue in favor of the validity of such generalization; the study merely tests it. For purposes of statistical analysis it is necessary to reduce psychiatric data to a classification of commonly recurring categories, in the terminology of common usage. The classification chosen has been such as to be readily identifiable by others.

Final decision as to the particular category in which a patient should be placed presented various difficulties, especially with patients who showed admixtures of traits. As there are no pure personality types, strict demarcation of boundary zones between categories depended on the application of clinical judgment in line with rather strict definitions. Some patients presented such a preponderance of certain traits that classification was easy. This applied particularly to some of the "neurotic" patients and the "psychopathic personalities." To be rated as "normal" the patient had to be a robust personality. The chief difficulty arose in consideration of the well integrated persons who showed slight degrees of neurotic traits or some other personality bias, such as exceptional egocentricity, irritability or sensitivity. Quantitation was in the last analysis a matter of clinical estimate. Some of the "normal" patients manifested on some occasions slight evidences of neurotic difficulties, but such episodes were so brief and transient as to have no influence on the general pattern of the personality. Those patients who, while free of characteristic neurotic symptoms, were somewhat more tense were classified as "essentially normal except for general nervousness." Particular difficulty involved the category of "personality variant." This included patients with definite bias in the personality, including particularly such traits as exceptional egocentricity, irritability, sensitivity and moodiness, but who, nevertheless, maintained a fairly stable and harmonious position in society. Obviously, the differences between such persons and "psychopaths" would be quantitative as well as qualitative. Exceptional sensitivity might well approach a paranoid level and indicate a categorical diagnosis of the schizoid type of psychopathic personality. Moodiness and emotionality might be so severe as to color the patient's relation to society and indicate a diagnosis of affective type of psychopathic personality. The diagnosis "personality variant," then, was based on the selection of patients who had such bias in the personality as to exclude them from the strictly "normal" group but who were not characteristically neurotic or psychopathic and whose bias was not that of simple general nervousness.

The main outlines of the categories which are presented here are offered in the following definitions:

Normal Personality.—A person who is in harmony with himself and his environment, is virtually free of psychoneurotic traits and other personality imbalances, is not habitually in conflict with the ethical and social standards of society, is free of addiction to alcohol, maintains satisfactory personal, social and occupational adjustments and presents a general integration of objectives and behavior. This does not exclude the possible existence of some personality bias, such as egocentricity or timidity, or even a history of brief or transient neurotic symptoms.

Psychopathic Personality.—A person who has shown extreme failure in social and intrapersonal adaptation, associated with impulsiveness, defective self control, lack of fixity of purpose, instability of effort and undependability in his work. In this category are wide variations. There may or may not be associated psychoneurotic phenomena. It is possible to make an unlimited series of subtypes of the psychopathic personality. We have selected seven: inferior, alcoholic, affective, aggressive, criminal, schizoid and miscellaneous types. As these subtypes are not discussed in the present study, they are not defined here.

Neurotic Personality.—A person whose behavior and experience are substantially affected by the existence

of traits or symptoms which characterize the generally accepted psychoneurotic syndromes of neurasthenia, hypochondriasis, anxiety neurosis, obsessional neurosis and hysteria.

Personality Variant.—A person who, while not psychotic, frankly psychoneurotic or psychopathic, has appreciably more weighting of the personality than the average normal subject. Such patients represent deviations from the average. The personality bias includes such traits as timidity, egocentricity, irritability, cantankerousness, hypersensitivity, moodiness, emotional lability, solemnity or general light heartedness.

Normal Adult Personality, but with Neurotic Traits in Childhood.—A well adjusted adult with a history of such neurotic traits in childhood as persistence of enuresis beyond infancy, nightmares, sleep walking and temper tantrums.

Normal Personality Except for General Nervousness.—A person of average personality, with some slight or special sensitivity, such as moderate emotional tension or a tendency to mild psychosomatic manifestations—for example, gastrointestinal symptoms, palpitation or perspiration—in association with emotional tension.

Behavior Problem in Childhood or Youth.—Persons who, without manifestation of intrinsic personality disorder (neurosis, psychopathy), had acted in a manner which was in acute conflict with the average standards of performance for his social group. Here would be included patients with a history of an isolated instance of delinquent behavior.

OBSERVATIONS AND CONCLUSIONS

Pretraumatic Personality Status.—The classification of the 200 patients on the basis of the categorical pretraumatic personality status is presented in table 1.

This distribution of personality categories probably represents an average for the portion of

TABLE 1.—*Pretraumatic Personality Status of Two Hundred Patients*

Diagnosis	Number of Patients	Percentage of Total Number of Patients
Normal personality	87	43.5
Psychopathic personality	34	17.0
Personality variant	31	15.5
Neurotic personality	17	8.5
Normal personality except for general nervousness	10	5.0
Mental deficiency	7	3.5
Neurotic traits in childhood	1	0.5
Psychotic behavior	1	0.5
Behavior problem (in childhood or youth)	1	0.5
Pretraumatic personality unknown	11	5.5

the population which is treated in large municipal hospitals. It should be noted that nearly half the number were considered essentially normal; approximately one sixth had psychopathic personalities; about the same number were personality variants, and about one twelfth of the patients had neurotic personalities.

Pretraumatic Personality in Relation to Post-Traumatic Mental Symptoms.—The post-traumatic psychiatric symptoms of each patient were carefully studied. It was found that prolonged failure to resume employment showed a higher correlation with the existence of mental symptoms than with any other symptom (headache, dizziness or direct physical sequelae). These post-traumatic mental symptoms have been discussed in detail by an associate.[9] They are mentioned here only for purposes of correlation with

TABLE 2.—*Distribution of Psychiatric Symptoms in a Series of Sixty-Four Patients with Post-Traumatic Mental Symptoms*

Symptom	Number of Patients
Anxiety states; apprehension	48
Fatigue (neurasthenia)	7
General nervousness	4
Hypochondriasis	2
Obsessive-compulsive neurosis	1
Depression	1
Euphoria	1

personality status. They may be listed and defined as follows:

Fatigue (neurasthenia): Complaints of tiring easily; a sense of exhaustion and lack of energy, and increased need for rest and sleep.

Nervousness; Inability to Concentrate: Pronounced tension with associated psychosomatic manifestations and inability to concentrate, without anxiety or other clearly neurotic disorder.

Fears; Anxiety; Panics: States of morbid, uncontrollable apprehension, either acute or chronic and of variable degree and duration. There may be associated somatic symptoms, and fatigue and nervousness may be present in addition.

Depression; Apathy: A predominant mood of depression or lack of concern with the usual objects of interest.

Hypochondriasis: Excessive preoccupation with and anxiety about the state of one's health, including specific anxiety about the head.

Obsessive-Compulsive Symptoms: The existence, singly or in combination, of obsessive, ruminative, compulsive, phobic or ritualistic phenomena.

Gross Change in Personality Only: Qualitative and quantitative deviation from pretraumatic patterns of personality and behavior not related to coexisting psychogenic changes, in particular in the absence of post-traumatic anxiety and other psychoneurotic states.

Euphoria: Elated, expansive mood with heightened sense of well-being.

In each case in which the patient showed any mental changes in convalescence the predominant symptoms were arbitrarily selected. Seventy patients (30 per cent) had post-traumatic men-

tal symptoms. It should be emphasized that the predominant mental symptom in convalescence is not the only one; virtually every patient presented more than one symptom. In fact, fatigability was present in a larger total number of patients than was any other symptom. However, it appeared of relatively minor importance, for in only 7 patients did it overshadow the other symptoms. Headache and dizziness were not taken into account.

Of the 70 patients who had post-traumatic mental symptoms, 64 (32 per cent of the total of 200 patients, or 90 per cent of the 70 patients) presented neurotic symptoms. The remaining 6 (3 per cent of the total of 200 patients, or 8.5 per cent of the 70 patients) showed a rather general personality change, without particular neurotic symptoms. Each of these 6 patients with general personality change had suffered an obviously severe injury to the brain, evidenced by such signs as prolonged coma and disorientation, prolonged deficit in performance tests, bloody spinal fluid, focal neurologic signs and indications for operation on the skull.

The distribution of the predominant psychiatric symptoms in our 64 cases is given in table 2.

The pretraumatic status of personality is correlated with the post-traumatic status in table 3.

From table 3 the following figures are taken for purposes of comparison:

Patients Presenting Post-Traumatic Mental Symptoms:

36% of 17 patients with pretraumatic neurotic personality.
35% of 34 patients with psychopathic personalities
30% of 31 patients with personality variants
29% of 7 patients with mental deficiency
30% of 87 patients with normal personality

These figures indicate that there is little, if any, correlation between the pretraumatic personality and the post-traumatic psychiatric symptoms. They certainly indicate that the pretraumatic personality is not a dominant factor in the production of post-traumatic symptoms.

It may be argued that a figure of 36 per cent for "neurotic" persons and of 35 per cent for "psychopaths" is significant as compared with a figure of 30 per cent for the entire series of 200 patients and for the group of 87 normal patients. While the small difference may be significant, it is certainly not sufficiently great to support any theory of post-traumatic neurosis which places the chief emphasis on the sole factor of pretraumatic personality. It should be noted that the highest incidence of post-traumatic mental symptoms (50 per cent) occurred in a group of 10 patients who were characterized as "essentially normal except for general nervousness."

The statements in the foregoing statistical analysis do not mean that the pretraumatic personality is never responsible for symptoms. In a particular case specific features of the pretraumatic personality may be the chief factor in the production of symptoms. But a comprehensive diagnosis of pretraumatic personality (such as "neurotic" or "normal") is not specific enough to indicate any probability of post-traumatic mental symptoms. This is supported by our observation that the highest incidence of symptoms appeared in the patients who were considered "essentially normal except for general nervousness." Of the total series of 200 patients, there were approximately 20, or 10 per cent, whose pretraumatic personality appeared to be of major significance in the production of post-traumatic mental symptoms. However, not more than 6 of these patients (3 per cent) were neurotic. Thus, while in certain cases the pretraumatic personality was believed to play a major role, the specific items were too subtle for generalization.

Relation Between Categorical Diagnosis and Clinical Impression.—Although the pretraumatic personality is generally not the sole factor in the

TABLE 3.—*Correlation of Pretraumatic and Post-Traumatic Personality Status*

Pretraumatic Personality Status	Number of Patients	Post-traumatic Personality Status: Free from Symptoms — Total Number of Patients	Free from Symptoms — Per Cent of Patients	Psychiatric Symptoms — Total Number of Patients	Psychiatric Symptoms — Percentage	Personality Change Only — Total Number of Patients	Personality Change Only — Percentage
Normal personality	87	61	70	26	30	0	0
Psychopathic personality	34	21	62	12	35	1	3
Personality variant	31	20	65	9	30	2	5
Normal personality with general nervousness	10	5	50	5	50	0	0
Neurotic personality	17	11	64	6	36	0	0
Mental deficiency	7	5	71	2	29	0	0
Neurotic traits in childhood	1	0	0	1	100	0	0
Psychotic behavior	1	0	0	1	100	0	0
Behavior problem	1	0	0	0	0	1	100
Unknown	11	7	64	2	18	2	18
Totals	200	130	65	64	32	6	3

causation of psychologic sequelae, there is little doubt that in many cases it contributes to a greater or lesser degree. In the final review of each case by the entire staff opinions were expressed as to the role of the pretraumatic personality in the production of sequelae. The clinician who handles a case builds up his impression from numerous items and details. The summation of impressions which go into the formation of an opinion are the result of implicit, as well as of explicit, perceptions. These opinions were clinical approximations reached after the event, and not to be confused with the categorical classification of all patients, regardless of the presence or absence of symptoms, dealt with in the preceding section. Since such clinical approximation is the routine approach to the problem in the clinic, its evaluation in relation to the present series of patients may be useful.

The full staff was in general agreement that the pretraumatic personality played some part in the production of psychologic sequelae in 58 (80 per cent) of the total of 70 patients with such sequelae. Reference to table 3 shows that approximately one half (26) of these patients had pretraumatic "normal" personalities and 32 had pretraumatic abnormal personalities. Virtually the same proportion is found among the 130 patients who did not have psychologic sequelae: The personalities of 61 were diagnosed as normal and those of 57 as abnormal (5 were mentally defective, and the previous personality of 7 patients was unknown).

Work History.—As Lewis [3] stated that the work history is of relevance in evaluation of pretraumatic personality, comment is pertinent. In the present series 146 patients had a satisfactory work history as judged by steadiness and continuity of employment, and 41 patients had an unsatisfactory work history. Of the 146 patients with a satisfactory work history, 93 (63 per cent) had no post-traumatic mental symptoms, and 53 (37 per cent) had such symptoms. Of a total of 41 patients who had no steady employment or had other unsatisfactory work records, 26 (63 per cent) had no psychiatric symptoms after injury, and 15 (37 per cent) had such symptoms. Thus the percentages are identical for the two groups and indicate that in itself the work history bears no relation to the presence or absence of post-traumatic mental symptoms.

Psychiatric Family History.—In discussing the liability of a personality to react, Symonds and Russell [1b] used the term "predisposition." They included not only the pretraumatic personality of the patient but the psychiatric history of his antecedents. In the present series there were 37 patients whose family histories gave evidence of neurosis, alcoholism, psychopathic personality, psychosis or similar disturbance. Of these, 26 (70 per cent) had no post-traumatic mental symptoms, and 11 (30 per cent) had such symptoms. Of 125 patients without a positive family history, 78 (62 per cent) had symptoms, and 47 (38 per cent) had no symptoms. Thus, there is a difference of only 8 per cent in favor of the development of post-traumatic mental symptoms in persons with a positive family history of psychiatric disorders. This difference is of doubtful significance.

Complicating Psychosocial Factors.—As the present paper is primarily concerned with the potential role of the personality a detailed discussion of the general causation of psychiatric sequelae of head injury is not attempted. It may be pointed out, however, that there was a high correlation between the continuance of psychiatric sequelae and the existence of associated situational factors. The latter included anxiety about returning to jobs in which the head injury had been sustained (firemen), fear in crossing streets, concerns about domestic difficulties, unsettled litigation and complicating injuries and illnesses.

TABLE 4.—*Complicating Psychosocial Factors and Post-Traumatic Mental Symptoms*

Complicating Factors, Regardless of Estimated Influence or Sequelae	Number of Patients	Patients with Symptoms	
		Number	Percentage
Litigation	34	22	64
Domestic troubles	18	7	40
Complicating injuries	28	9	32
Occupational difficulties	11	8	75
Financial difficulties	8	2	25
Selective service	5	2	40

One hundred and four patients presented a variety of complicating factors (table 4).

According to this table, there is a substantial correlation between the existence of litigation, on the one hand, and the development of psychiatric sequelae (64 per cent), on the other. Under "occupational difficulties" one will note that of 11 patients 8 (75 per cent) had sequelae. They were men engaged in a hazardous occupation (firemen) who had witnessed the deaths of some of their fellows. All these patients were receiving full salary while ill. Thus, for them to remain ill meant a continuation of their safe status. In that respect they could be compared to soldiers who had failed to recover. Thus, this group could well be classified with the litigation group, so that a total of 45 patients

had an intelligible motive (conscious or unconscious) for remaining sick, of whom 30 (66 per cent) did have mental symptoms. There is a higher correlation here than with the pretraumatic personality type or with any other factor in this study.

To test a possible chance relation, the pretraumatic personality status was correlated with the existence of complicating factors. From these correlations it appears that complicating factors were presented by 53 (60 per cent) of the 89 "normal" patients, by 10 (59 per cent) of the 17 "neurotic" patients, by 20 (59 per cent) of the 34 "psychopaths," by 22 (70 per cent) of the 31 patients with "personality variant" and by 6 (60 per cent) of the 10 patients with "normal personality except for general nervousness." The average incidence of complications for the entire series of 200 patients was 62 per cent. These figures indicate a distribution which excludes the factor of chance in the conclusion that there is a high correlation between the existence of psychiatric sequelae and psychosocial complicating factors.

COMMENT

No author, to my knowledge, has asserted that the pretraumatic personality is exclusively responsible for the development of psychologic sequelae of head injury. The view that pretraumatic personality may be largely responsible for the psychiatric sequelae of head injuries was epitomized by Symonds with the conclusion that ". . . it is not only the kind of injury that matters, but the kind of head." [8a] Later, Symonds and Russell expressed the conviction that "the mental constitution before injury plays an important part in the prognosis of head injuries." [1b] They mentioned "predisposition to mental disorder . . . evinced by the family or personal history of the individual." In a group of military patients they found that "predisposition" was twice as common among the men with chronic illnesses as among those with short illnesses. Also, twice as many men were invalided from the group with predisposition as from the group which showed no predisposition. They noted, however, that 33 per cent of the group with predisposition to mental disorder returned to active service, that predisposition in itself did not carry a bad prognosis but that among the factors having an adverse effect on recovery from head injury the role of predisposition was of significance. They stated further:

> Our data therefore suggest that if two men of dissimilar mental constitution suffer head injury of comparable severity, as judged by the duration of the PTA [post-traumatic amnesia], the prognosis is much worse for the man with a latent or evinced liability to mental disorder.

Lewis [3] reached a similar conclusion from a study of 64 patients with head injury whose symptoms had persisted so long as to be looked on as chronic and the character of whose symptoms was such that they had been transferred to a "neurosis center." Lewis compared these patients suffering from head injury with 64 neurotic patients without head injury in the same hospital. The latter group had been especially selected to match the group with head injury in that they "exhibited the clinical syndromes in the same proportions as did the head injury cases. Thus, there were 16 patients with conversion hysteria in each group, 2 patients with hysterical amnesia, 6 with a severe acute anxiety state, 14 with a chronic anxiety state, and so on." These groups were compared with respect to a number of attributes of psychiatric interest, including family history, occupational and personal history, previous personality, present illness and symptoms thereof. In evaluation of the previous personality, only twelve types were considered: stable, weak, delinquent, inert, rebellious, suspicious, cyclothymic, schizoid, hysterical, anxious, hypochondriacal and obsessional. Lewis concluded:

> . . . the long-standing, relatively intractable post-contusional syndrome is apt to occur in much the same person as develops a psychiatric syndrome in other circumstances without any brain injury at all.

Lewis took note of possible objections to the use of his group with head injury as representative of the "minor contusional syndrome" (Symonds' equivalent of the term "post-concussion syndrome"). His group had been selected from patients with head injury because of the chronicity of symptoms which were recognized as characteristically neurotic. It is obvious that conclusions derived from a study of such a group cannot be applied to the general group of patients with post-traumatic mental sequelae. But even in his group it was noted that 36 (56 per cent) of the patients with head injury who were invalided because of neurotic sequelae had pretraumatic "stable" personalities, whereas in the group of "neurotic" patients who had not sustained head injury only 25 per cent had had previously stable personalities.

It should be emphasized that neither Symonds nor Lewis ascribed the development of psychiatric sequelae exclusively to a pretraumatic personality. Both pointed out that the reaction of the personality to immediate organic features of the head injury, such as dizziness and head-

ache, was unquestionably a factor, and they also took note of the undoubted influence of complicating situational stresses arising out of or relating to the injury. They also emphasized the motivation, undoubtedly subconscious, which might perpetuate symptoms when recovery from such symptoms would be followed by return to active military service. The chief difference between their observations and the results of the present study relates to the weight to be attached to the pretraumatic personality.

Schilder [5] pointed out, as did Symonds and Russell [1b] and Denny-Brown,[10] that the experiences directly referable to physical trauma to the brain, such as headache and dizziness, in themselves contribute to the development of neurotic reactions. Of additional interest is his insistence that neuroses associated with trauma to the head should be distinguished from neuroses associated with trauma to other parts of the body. He demonstrated that the cause of the two types of neurosis may be quite different; that special value is set by the patient on his head, particularly his brain, and that the physical symptoms associated with head injury (dizziness, instability) produce a sense of insecurity, with associated anxiety. Schilder did not place any special weight on pretraumatic personality. He stated:

> Traumatic neurosis in general, and neurosis after head injuries, may occur in individuals who were neurotic previously or had neurotic tendencies; or it may occur in individuals who were not neurotic in the commonly accepted sense before the accident.

Denny-Brown [10] maintained that persistent disability (sequelae) in the individual case must be evaluated in terms of both physiologic and psychologic factors. He stated:

> Too frequently, emphasis is laid wholly on either structural damage or psychoneurotic state, with consequent failure to achieve the best results from treatment of both. Although particularly evident to the trained neurologist by reason of his familiarity with both functional and organic nervous disorders, the proportions of the mixture should be evident to anyone who takes time to sum up the pretraumatic nervous constitution and personality, the severity of the general brain injury, the residual intellectual and physical state, and the nature and degree of persistent anxiety.

From our data it appears that there is little, or no, correlation between pretraumatic personality and the liability to development of post-traumatic mental symptoms. A patient with a pretraumatic "neurotic" personality may be free from symptoms. A patient with a pretraumatic "normal" personality may be crippled by mental symptoms. This does not mean that the pretraumatic personality may not play a large, or even the sole, part in the production of post-traumatic mental symptoms. It does mean that the development of post-traumatic mental symptoms may not generally be ascribed to the pretraumatic personality. There is no general rule that patients with over-all neurotic or psychopathic personalities are more likely to manifest symptoms after trauma than are normal persons.

SUMMARY

In 200 cases of head injury the categorical pretraumatic personality was found to have little, if any, correlation with the incidence of post-traumatic mental symptoms. There was a significant correlation between the incidence of post-traumatic mental symptoms and the existence of complicating psychosocial factors.

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10. Denny-Brown, D.: The Sequelae of War Head Injuries, New England J. Med. **227**:771-780 and 813-821, 1942.

EFFECT OF SODIUM AMYTAL AND AMPHETAMINE SULFATE ON MENTAL SET IN SCHIZOPHRENIA

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It usually is stated that schizophrenia is characterized by three primary symptoms: a disturbance in attention, a disturbance in the association of ideas and a disturbance in affect. The other features of this disorder are regarded as secondary elaborations of these primary symptoms. The relationships among the primary symptoms and between the primary and the secondary symptoms are of interest from a variety of standpoints: etiologic, diagnostic, prognostic and psychopathologic. Increased interest in these topics followed the reports of Lindemann [1] that sodium amytal injected intravenously in smaller than sleep-producing amounts often caused a profound change in the mental status of a patient, sometimes temporarily changing his reactions to relatively normal ones. Thus, in the case of schizophrenia, the attention may be improved, the thought processes may become more logical and the affect may appear more adequate. There is also an increased ease of communication, so that the patient may reveal the content of his psychosis. Furthermore, under the influence of the drug, some patients show improvement in but one or two of the primary symptoms, and, finally, some patients show little or no change. This drug, then, affords an opportunity to study the relation among the symptoms and to investigate problems of diagnosis, of etiology and of prognosis. For example, Gottlieb and Hope [2] stated that a good response to sodium amytal was related to a favorable prognosis, and Layman [3] reported that the performance of a group of patients on a battery of psychologic tests was improved by the drug. It would be desirable to have quantitative measures of changes in the primary symptoms, so that these problems could be investigated with greater exactness. Some beginnings have been made in this direction. The use of certain psychometric tests has redefined the whole problem of schizophrenic thinking.[4] Similarly, a technic for measurement of reaction time has been developed which may be used to measure the disorder in attention.[5] The present report deals with the question: Can the clinical improvement in attention produced by intravenous administration of sodium amytal in schizophrenic patients be measured by this reaction time technic?

The technic of measuring attention is more specifically referred to as a method of measuring mental set. The latter term is preferable, since it has a more precise meaning than attention. In terms of the experimental technic, mental set means the ability to maintain an orientation toward certain environmental stimuli at a high level. The procedure involves measuring the subject's reaction time to an auditory stimulus under two types of conditions. In one condition a warning or preparatory signal is presented at constant temporal intervals before each reaction signal (regular procedure). In the second condition the length of the preparatory interval between the warning and the reaction signal is varied haphazardly (irregular procedure). In the first condition a normal subject will profit by the constant interval between the two signals and will be prepared to react quickly. In the second condition his reaction times are longer, apparently because he does not know when to expect the reaction signal. Furthermore, in the

1. Lindemann, E.: The Psychopathological Effects of Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **28**:864, 1931; Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **11**:1083-1091, 1932. Lindemann, E., and Malamud, W.: Experimental Analysis of the Psychopathological Effects of Intoxicating Drugs, ibid. **13**:853-879, 1934. Lindemann, E.: The Neurophysiological Effect of Intoxicating Drugs, ibid. **13**: 1007-1037, 1934.

2. Gottlieb, J. S., and Hope, J. M.: Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **46**:86-97 (July) 1941.

3. Layman, J. W.: A Quantitative Study of Certain Changes in Schizophrenic Patients Under the Influence of Sodium Amytal, J. Gen. Psychol. **22**:67-86, 1940.

4. Kasanin, J. S.: Language and Thought in Schizophrenia, Berkeley, Calif., University of California Press, 1944.

5. Huston, P. E.; Shakow, D., and Riggs, L. A.: Studies of Motor Function in Schizophrenia: II. Reaction Time, J. Gen. Psychol. **16**:39-82, 1937. Rodnick, E. H., and Shakow, D.: Set in Schizophrenia as Measured by a Composite Reaction Time Index, Am. J. Psychiat. **97**:214-225, 1940.

regular procedure, as the length of the preparatory interval is increased to about fifteen or twenty seconds, the advantage of a constant interval is lost, and the reaction times approximate those of the irregular procedure. Curves plotting reaction time as a function of the preparatory interval show a separation of the curves for the two procedures with intervals below fifteen or twenty seconds in a normal group, the curve for the regular procedure representing faster reactions than the curve for the irregular procedure. Schizophrenic subjects, on the other hand, fail to profit by a knowledge of the length of the preparatory interval to the same degree that normal subjects do. As a consequence, similar curves for a schizophrenic group show a separation of the curves for the regular and the irregular procedure only for intervals below about five seconds. With longer preparatory intervals curves for the patients tend to run together. Hence it has been suggested that schizophrenic patients do not maintain a mental set as well as normal persons.[5]

MATERIALS AND METHODS

Nine schizophrenic patients and 9 normal control subjects were used in this study. The patients had all been recently admitted to the Iowa State Psychopathic Hospital, though the average duration of the psychosis was nine months. They had a mean age of 28.5 years, with a range from 16 to 49 years. Two were women and 7 were men. The clinical subtypes were distributed as follows: paranoid, 1; hebephrenic, 3; simple, 1, and unclassified, 4. All the patients were in good contact with the environment and were cooperative in the experimental situation. The control subjects were university students. Their mean age was 22.8 years, with a range from 20 to 26 years. Six were women and 3 were men.

The apparatus consisted of a flashlight bulb to serve as a warning signal, a buzzer to which the subject reacted by slipping his index finger off a telegraph key, an electrical chronoscope calibrated in hundredths of a second to measure the reaction time and a device to control the length of the preparatory intervals. This device was a synchronous motor polygraph which drove a punched paper tape. Completion of an electrical circuit through holes in the tape flashed the warning light and, at the end of the proper preparatory interval, sounded the buzzer. Simultaneously with the sounding of the buzzer the chronoscope started. It was stopped when the subject reacted. Five preparatory intervals were used: two, three and a half, five, ten and twenty seconds. These were presented in two ways. In the regular procedure all the reactions to any preparatory interval were given together. The order of presentation by intervals was: three and a half, ten, five, two and twenty seconds. Twenty reactions to each interval were taken. After each group of twenty reactions, the subject was told a new interval was to be used. In the irregular procedure the preparatory intervals were presented at random until twenty reactions to each interval were obtained. In this procedure the time between a reaction and the next warning signal also varied. Practice sessions of ten reactions were given before both the regular and the irregular procedure. The instructions to the subject were worded so as to orient him toward the reaction movement rather than the stimulus, since "muscular" reactions are shorter and less variable than "sensorial" reactions.[6] Rest periods of about two minutes were given after each twenty reactions in both procedures. Each procedure took about forty-five minutes. The irregular procedure was performed before the regular one in each session.

Each subject was tested four times: In sessions 1 and 2 there was no medication. In sessions 3 and 4 each subject received 250 mg. of sodium amytal and 10 mg. of amphetamine sulfate intravenously. The latter drug combats the sedative effect of sodium amytal, so that more time-consuming experiments may be performed.[7] It should be noted that a maximal effect in each subject with a standard dose of the drugs would not be expected. However, the present study was preliminary, and it was thought that if changes in mental set could be measured by the suggested technic, the effect should be revealed with somewhat smaller than maximal doses. After the drugs were injected, a period of thirty minutes was allowed for the acute effects to wear off. In the final analysis of the results, session 2 (without amytal) was compared with session 4 (with amytal). This was done to yield somewhat less variable material. Session 1 seemed to show some practice effects, as did the first session with amytal (session 3). However, the general picture of the results remained the same regardless of what sessions with or without amytal were used for comparison. Owing to tearing of the punched paper tape on humid days and occasional failure of a subject to hold the telegraph key down for subsequent reactions, twenty reactions per preparatory interval were not obtained for every subject. Thus, from fifteen to eighteen reactions per interval were used in the statistical analysis, with each subject serving as his own control with respect to the number of reactions per interval. The average number of reactions per interval for all subjects was seventeen.

RESULTS

Without Drugs.—The performances of the two groups can be compared by examination of table 1 and figure 1, in which means for the group, standard deviations of the means and mean coefficients of variation are tabulated and plotted for the condition without amytal.

From this material it may be seen that the mean reaction time of the patient group is longer than that of the control group in both procedures for all preparatory intervals. The differences between the two groups are statistically significant at the 1 per cent level of confidence at each preparatory interval for the corresponding procedures.

A more interesting comparison is that the curves for the two procedures in the patient group cross, while in the normal group the curves are separate for all preparatory intervals, the means

6. Woodworth, R. S.: Experimental Psychology, New York, Henry Holt & Company, Inc., 1938, pp. 306-308.

7. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions, Arch. Neurol. & Psychiat. **51**:260-263 (March) 1944.

for the regular procedure being always shorter. In the patient group at the two second interval the difference in the two procedures yields a statistical level of confidence of 2 per cent, but at all other intervals the differences are not significant enough to warrant statistical confidence. These figures are 2, 40, 60, 20 and 80 per cent for the two, three and a half, five, ten and twenty second intervals respectively. For the control subjects, on the other hand, the levels of confidence for the differences between the two procedures are 1, 1, 2, 5 and 70 per cent for the two, three and a half, five, ten and twenty second intervals respectively. These levels of confidence for the control group are a reflection of the fact that as the preparatory interval increases in length the means of the regular procedure approach those of the irregular procedure.

These findings confirm the results of previous experiments of this type.[5] They are interpreted to mean that normal subjects are able to maintain the set to react at a higher degree when a preparatory interval of constant length (regular procedure) is used than when the preparatory interval varies haphazardly (irregular procedure). As the interval increases in length, however, it becomes increasingly difficult to hold the set to react at a high level of preparation, and the means of the regular procedure approach those of the irregular procedure. In the patients, on the other hand, the ability to maintain the set to react is poorer; the differences between the means of the procedure are less at the shorter intervals than those for the control subjects, and the curves of the two procedures join or cross at shorter intervals (fig. 1).

With Drugs.—The behavior and the spontaneous comments made by each subject during the amytal sessions were recorded. After injection of the drugs the control subjects complained of light headedness, blurring of vision and slight numbness and weakness of the arms and legs. Their gait was somewhat unsteady and speech was slow and slurred. They were extremely talkative and stated that they felt less motivated to do well in the experiment and that it was more difficult to keep oriented toward the task. The patients complained of similar initial changes, but they verbalized these less than the control subjects. Objectively, they were more talkative and seemed to have increased social and self confidence after injection of the drugs. Their speech content tended to be more relevant, their attention better and their affect warmer.

TABLE 1.—*Mean Reaction Times, Standard Deviations and Mean Coefficients of Variation in Hundredths of a Second by Preparatory Intervals for Regular and Irregular Procedures Without Sodium Amytal*

	Preparatory Intervals														
	2 Seconds			3.5 Seconds			5 Seconds			10 Seconds			20 Seconds		
	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.
Patient Group															
Regular procedure	31.66	6.85	12.91	32.33	5.16	14.53	33.10	6.92	12.15	36.12	7.61	15.24	35.56	6.90	16.30
Irregular procedure	33.62	5.48	16.26	33.27	5.29	16.16	33.67	5.73	14.74	33.70	5.75	17.41	35.22	6.43	14.45
Control Group															
Regular procedure	20.13	2.80	14.80	21.18	2.98	13.20	22.44	4.02	13.49	23.06	3.83	14.25	25.25	4.05	12.03
Irregular procedure	26.88	2.82	14.30	25.41	2.85	12.40	25.47	2.99	12.15	25.84	2.51	13.54	25.73	2.61	14.78

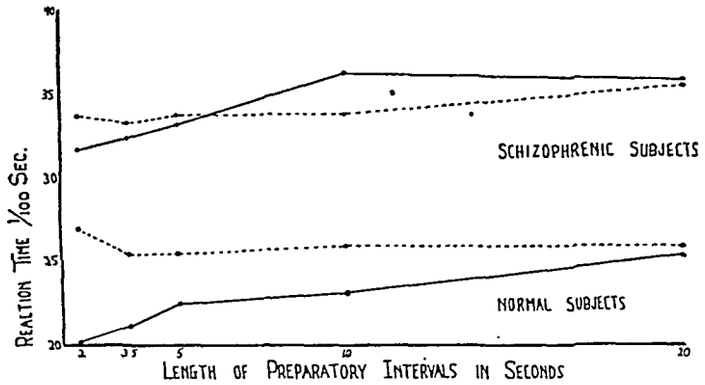

Fig. 1.—Mean reaction times of schizophrenic and normal subjects without sodium amytal. In this figure, and in figure 2, the curve for the regular procedure is an unbroken line; the curve for the irregular procedure, a broken line.

Table 2 and figure 2 present the mean reaction times, the standard deviations of the means and the mean cofficients of variation by intervals for both procedures with amytal.

The effect of the drug in the normal group was to increase the reaction time in both procedures for every preparatory interval. The shortest reaction times were found in this group with the shortest preparatory intervals of the regular procedure. The curve of the regular procedure shows a tendency to rise as the preparatory intervals increase. The mean values for the irregular procedure are everywhere longer than those for the regular procedure. The differences between

the means of the two procedures have statistical levels of confidence of 1, 1, 5, 20 and 10 per cent for the one, two, three and a half, ten and twenty second intervals respectively. In general, then, the normal group produced curves of the means with amytal very similar to those without amytal except that both curves with amytal represented slower reaction times than the curves without amytal. This is interpreted as meaning that under amytal sedation these subjects were still able to profit by a constant preparatory interval and reacted more quickly than with random variations of the preparatory interval.

In the group of patients the curve of the regular procedure shows a gradual rise with increasing length of the preparatory interval. The curve of the irregular procedure is practically flat. The point of special interest about these curves is that they are separate for all preparatory intervals, producing a picture similar to that for the control subjects. The statistical levels of confidence which attach to the differences in means of the two procedures are 2, 20, 10, 20 and 5 per cent for the two, three and a half, five, ten and twenty second intervals respectively. These values are in considerable contrast to those found in the condition without amytal.

Is the separation of the curves of the patient group primarily caused by a change in the regular or in the irregular procedure? Examination of the mean values shows that the principal effect of the amytal was to shorten the reactions in the regular procedure to the longer intervals, i. e., to the five, ten and twenty second intervals, while the reactions to the two and three and a half second intervals revealed little difference between the situation with amytal and that without amytal. In the irregular procedure there was a slight tendency for the means to be longer with than without amytal. These results seem to indicate that the patients were able, under the influence of the drug, to profit primarily from the constant preparatory intervals and to maintain a better readiness to react.

Examination of the standard deviations of the means (tables 1 and 2) indicates that the patients as a group showed more variability for all intervals than did the control subjects. In both groups the effect of amytal was to increase the variability for all intervals in both procedures. The means of the coefficients of variation, which express variability in relation to the magnitude of the means, indicate that the effect of amytal was to make the reactions of the control group and those of the patients somewhat more consistent with their own mean values.

It is interesting, also, to survey individual performances in the two groups. In the condition without amytal, 1 patient had shorter reaction times in the regular procedure than in the irregular procedure for every preparatory interval. This patient was the most normal clinically. Another patient who had not received amytal showed no separation of the curves of the two procedures for either short or long intervals. For the remaining 7 patients the curves for the shorter intervals were separated but those for the longer intervals were merged. With amytal, however, 5 patients had separation of the curves of the two procedures for all intervals; 2 patients, for every interval but one, and 2 patients, for three of the five intervals. Of the control subjects without

TABLE 2.—*Mean Reaction Times, Standard Deviations and Mean Coefficients of Variation in Hundredths of a Second by Preparatory Intervals for Regular and Irregular Procedures with Sodium Amytal*

	Preparatory Intervals														
	2 Seconds			3.5 Seconds			5 Seconds			10 Seconds			20 Seconds		
	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.	Mean	S. D.	C. V.
Patient Group															
Regular procedure	31.78	8.41	11.17	32.34	8.44	10.77	32.35	8.33	10.75	32.93	8.13	10.86	33.46	7.88	13.36
Irregular procedure	35.87	7.19	13.01	33.82	7.26	11.10	34.62	8.05	12.81	34.78	7.54	12.10	35.95	7.11	15.55
Control Group															
Regular procedure	23.02	4.30	14.49	23.76	4.90	12.64	24.41	5.46	10.52	25.97	5.59	12.89	26.33	5.13	11.17
Irregular procedure	25.84	5.31	14.61	27.83	5.41	13.21	28.28	5.25	13.21	28.04	5.29	13.09	28.69	5.07	13.24

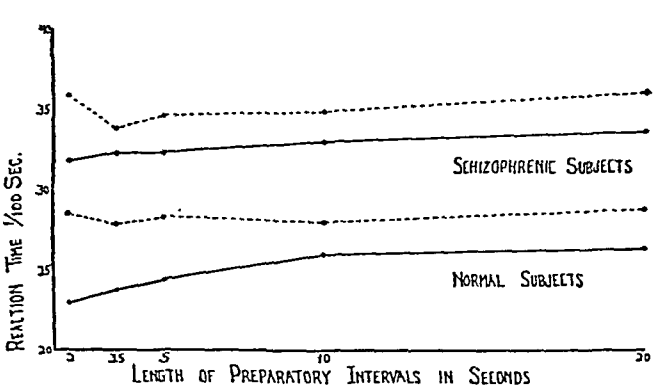

Fig. 2.—Mean reaction times of schizophrenic and normal subjects with sodium amytal.

amytal, the curves for 3 were separated for all intervals; for 3 others, through the ten second intervals, and for 1 through the five second interval. The curves for 1 control subject tended to merge after the three and a half second interval, and for 1, after the two second interval. Of the control subjects with amytal, the curves were separated throughout for 6, through the ten second interval for 1 and through the five second interval for 2.

SUMMARY AND CONCLUSIONS

The present experiment was performed in an attempt to quantify the improvement in attention (mental set) observed clinically in schizophrenic patients who have received intravenous injections of sodium amytal. The auditory reaction time was obtained under two types of conditions. In one condition, the regular procedure, the length of the preparatory interval, i. e., the time between a visual warning signal and the auditory reaction stimulus, was constant for all the reactions to that interval. In the second condition, the irregular procedure, the length of the preparatory interval varied haphazardly. Five preparatory intervals were used: two, three and a half, five, ten and twenty seconds. Nine schizophrenic patients and 9 normal persons served as subjects. Each subject was tested with and without intravenous administration of 250 mg. of sodium amytal and 10 mg. of amphetamine sulfate.

Our results confirm the work of earlier investigations in which no drugs were used. The reaction time of the patient group was significantly longer than that of the control subjects in both procedures. The control group reacted more quickly in the regular procedure than in the irregular procedure for all preparatory intervals. The patient group failed to react more quickly in the regular procedure after the five second preparatory interval. With medication the normal group continued to react more quickly in the regular procedure than in the irregular procedure for all preparatory intervals. The patient group, with medication, had reaction times which were significantly longer in both procedures than those of the control group. However, in contrast to their behavior without medication, they now reacted more quickly in the regular procedure than in the irregular procedure for every preparatory interval.

It is concluded from these results, first, that the schizophrenic patients as a group suffer from inability to attain as high a level of mental set as do normal subjects and that they do not maintain the level of preparation they attain as long as controls. Second, the reaction time technic may be used to measure one aspect of the improvement seen clinically (improvement in attention) in schizophrenic patients when sodium amytal is injected intravenously. Third, the improvement is such as to produce a normal relationship between the reaction times of the regular and those of the irregular procedure.

Dr. J. R. Knott assisted in constructing the apparatus, and Dr. C. R. Strother gave statistical advice.

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EFFECTIVENESS OF DIPHENYLHYDANTOIN IN MANAGEMENT OF NONEPILEPTIC PSYCHOMOTOR EXCITEMENT STATES

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The present report is based on an investigation by Kalinowsky and Putnam [1] which revealed that diphenylhydantoin sodium is capable of producing distinct changes in behavior in nonepileptic psychotic patients. In view of the observations of Blair, Bailey and McGregor [2] and of McEachern,[3] who found that this drug could transform querulous, moody and irritable epileptic patients into pleasant, agreeable and congenial persons, it seemed appropriate to study the effect of diphenylhydantoin on certain mental symptoms of other origin. Kalinowsky and Putnam selected 60 patients representing chiefly cases of schizophrenia and manic-depressive psychosis. The duration of the treatment was from two to five weeks, during which time all other therapeutic methods, including psychotherapy, were purposely omitted, so that the effects of diphenylhydantoin could be accurately observed. The initial daily dose was usually 3 to 4 capsules of diphenylhydantoin sodium, 0.1 Gm. (1½ grains) each. After two days the dose was increased to 5, and later to 6, capsules daily. Improvement occurred in more than 50 per cent of the patients during the period of treatment. This improvement was manifested by diminution of excitement and psychomotor hyperactivity almost irrespective of the type of psychosis. The authors concluded that diphenylhydantoin sodium has a purely symptomatic action on states of excitement in various psychoses and recommended further study of the usefulness of the drug for psychotic states.

PRESENT INVESTIGATION

The following report is based on a prolonged observation of the behavior patterns of a variety of nonepileptic psychotic patients who were treated with diphenylhydantoin sodium. It was originally intended to select a large group of patients consisting of clinic patients under treatment for various psychoneurotic states of tension and excitement and of hospital patients representing the major psychoses. This plan, however, had to be abandoned, since a number of selected clinic patients did not report regularly enough to permit reliable conclusions. Furthermore, a proper evaluation of the effect of the drug on a number of hospital patients proved difficult because the behavior pattern of these patients was not well enough known. Kalinowsky and Putnam stressed the difficulty of judging results in treatment of mental disorders. Since many states of excitement in psychotic patients subside spontaneously, it is often impossible to attribute favorable responses to the specificity of a drug or of any kind of treatment. It was therefore decided to obtain the highest possible degree of accuracy in evaluating the effect of diphenylhydantoin by selecting a smaller number of patients and studying their behavior pattern previous to, during and following treatment with the drug.

Forty patients were chosen for this investigation, which lasted one year. Special behavior charts were devised to register every kind of activity and change in attitude on a daily basis. Every patient was seen twice daily, and additional observations were made by the specially instructed ward nurses. Capsules of diphenylhydantoin sodium, 0.1 Gm. (1½ grains) each, were used exclusively. The importance of individualizing the dose of the drug was soon recognized. The initial daily dose varied from 3 to 5 capsules. In cases of acute manic or catatonic excitement the larger dose was used at the start of the treatment. In cases of less acute excitement the dose was gradually increased from 3 to 6 capsules over a period of from three to six days. The maximum daily dose was 6 capsules.

The average duration of the treatment was from two to five weeks. The patients who showed the best responses had repeated courses of treatment with the drug during the year of observation. The repetition of the treatment seemed the best method of eliminating coincidental factors from evaluation of the effectiveness of the drug.

For the 40 selected patients the following diagnoses had been made:

Manic-depressive psychosis, manic type	6
Schizophrenia, catatonic type	14
Schizophrenia, paranoid type	7
Schizophrenia, hebephrenic type	4
Mental deficiency, excitement states	6
Dementia paralytica, excitement states	2
Postencephalitis, excitement state	1
	40

From Delaware State Hospital.

1. Kalinowsky, L. B., and Putnam, T. J.: Attempts at Treatment of Schizophrenia and Other Nonepileptic Psychoses with Dilantin, Arch. Neurol. & Psychiat. 49:414 (March) 1943.

2. Blair, D.; Bailey, K. C., and McGregor, J. S.: Treatment of Epilepsy with Epanutin, Lancet **2**:363, 1939.

3. McEachern, D.: Epilepsy, Canad. M. A. J. **45**: 106, 1941.

The patients were chosen according to the presence of phenomena of psychomotor excitement, which they had in common regardless of the type of psychosis. The selection was arbitrary, as many patients who would have been excellent subjects for this study had to be excluded because they did not cooperate well enough to take the drug regularly. In the following analysis of the data of this study, more emphasis is placed on the types of responses than on statistical evaluation of the material. A purely statistical analysis would not do sufficient justice to the differences in the individual psychopathologic phenomena and would be handicapped by the relatively small total number of patients. The experience with these patients leads to the conclusion that it is the quality of responses rather than the number of improved patients which provides material for evaluation of the efficacy of diphenylhydantoin sodium in the treatment of nonepileptic psychoses.

ANALYSIS OF DATA

Affective Psychosis.—Of the group with manic-depressive psychoses, 4 patients showed doubtful responses. Manic excitement disappeared during the weeks of treatment with diphenylhydantoin; the improvement, however, was neither prompt nor necessarily specific, since each of these patients showed spontaneous remissions of manic attacks during the one year period of observation. The fifth patient responded promptly and had complete disappearance of manic excitement; the manic phase was followed almost immediately by a depression, which did not respond to diphenylhydantoin. The sixth patient, differing from the others in the manifestations of the psychosis, showed a most favorable response to the drug, which proved to be specific, as could be demonstrated during four courses of the treatment. This case will be described in detail because it illustrates some essential facts about the type of patient who is most responsive to diphenylhydantoin.

CASE 1.—The 54 year old white woman, M. A., had been in a perpetual state of pronounced motor restlessness since she was admitted to the Delaware State Hospital, four years prior to this report. She was born in Poland, and facts about her personal and family history are scant. She is known to have been restless, moody and irritable throughout her life. After the death of her husband, in 1940, she became overactive and began to talk in a flighty and irrelevant fashion. She sang and danced almost constantly, refused to go to bed at night, became generally unmanageable and was admitted to the Delaware State Hospital Feb. 26, 1941. On admission she appeared elated, was very restless and sang, danced and exposed herself on every possible occasion. She grew steadily more excited and had to be transferred to a ward for disturbed patients. Neither hydrotherapy nor metrazol or electric shock therapy influenced the excitement state effectively. It became necessary to restrain her and to control her immense restlessness with strong doses of sedatives, as she would climb up window screens and turn somersaults with such violence that she sustained bruises and abrasions all over her body. She masturbated excessively in an exhibitionistic manner.

Medication with diphenylhydantoin sodium was initiated with 4 capsules, but the dose was increased to 6 capsules within three days. Her condition remained without significant change for the first eight days and then showed a steady decrease of motor activity. Restraints became unnecessary as the patient was able to sit in a chair without signs of restlessness. She cooperated well for the first time since her admission to the hospital. Other phenomena of her psychosis, such as elation and flightiness of associations, remained unchanged. This striking improvement was not maintained for more than four or five days after the medication was discontinued. She again became extremely disturbed and remained so in spite of another course of electric shock treatment. Treatment with diphenylhydantoin was resumed after an interval of two months; again the patient showed prompt improvement. Two more courses of treatment with the drug were given, and equally satisfactory results were obtained, as psychomotor disturbances were notably decreased and the patient was able to adjust to the ward life while being treated with the drug. Since no spontaneous remissions occurred at all, the disappearance of psychomotor excitement can be attributed to the specific action of diphenylhydantoin.

Schizophrenic Psychosis.—Kalinowsky and Putnam obtained the best responses with catatonic excitement states. The same observation was made in this investigation. Catatonic patients with sudden outbursts of assaultive and destructive behavior, with screaming spells or sexual excitement, reacted by far more favorably than patients with predominantly negativistic, stuporous behavior, who were essentially uninfluenced. In the schizophrenic group, 3 patients showed pronounced improvement; 3, moderate improvement, and the rest failed to exhibit any appreciable change in behavior. Closer study of the phenomena of the psychoses of these patients suggests that persons whose psychomotor excitement is caused by the fundamental, primary disturbance of the disease process react more favorably than those whose excitement state is a reaction to the accessory, psychogenic factors. The following case represents such a type of primary psychomotor excitement.

CASE 2.—The 36 year old white woman, R. C., had been in the Delaware State Hospital since Nov. 6, 1930. The family history is noncontributory except for the fact that her father is described as "excitable and peculiar." As a young girl the patient was reserved and shy and showed early signs of increasing introversion. She became seclusive after leaving school, had spells of complete withdrawal and expressed bizarre and persecutory ideas. Temper tantrums and fainting spells are mentioned in her history. In the hospital she frequently had states of psychomotor excitement. During the past few years she had been mute, assumed rigid postures, masturbated excessively and screamed wildly

when approaching orgasm. She was always extremely tense and attacked other patients in an explosive fashion. There was no favorable response to shock treatments.

Treatment with diphenylhydantoin sodium was started with 5 capsules daily. The amount was increased to 6 capsules daily within three days, and this dose was maintained for four weeks. The patient went into a state of catatonic stupor and had complete disappearance of psychomotor activity. She stopped masturbating and remained completely passive. When medication was discontinued, she again showed all the features of catatonic excitement. Another course of treatment with the drug was started after an interval of two months; again, an almost total disappearance of psychomotor activity was observed. Diphenylhydantoin stopped the urge to masturbate, a practice in which the patient had been engaged almost constantly and which had proved refractory to hydrotherapy, shock treatments and administration of sedatives. The impression was conveyed that excessive masturbation in this case was primarily a symptom of the generalized psychomotor excitement and to only a minor degree an expression of autoerotism. Similar observations during treatment with diphenylhydantoin were made on a number of patients.

The paranoid patients did not show any significant improvement. In this group the excitement was usually a secondary reaction to manifestations of the psychosis, to ideas of persecution or to auditory or visual hallucinations and remained uninfluenced by treatment with diphenylhydantoin. Daily observations on these patients showed such variety in precipitation and duration of excitement states that in the few cases in which a decrease of excitement occurred during the period of treatment it did not seem justified to give the credit to diphenylhydantoin.

Of the hebephrenic patients, 1 showed moderate improvement. This woman was overactive, gave silly performances of dancing and grimacing and showed occasionally assaultive tendencies. During treatment with diphenylhydantoin she became distinctly more passive and appeared preoccupied. The course of treatments could not be repeated, as the patient, again overactive and silly, refused to take the drug regularly.

Excitement States Accompanying Mental Deficiency.—For six patients the diagnosis of mental deficiency with psychosis was made. For psychiatric purposes, this classification lacks differentiation of the psychopathologic manifestations. It seems appropriate, therefore, to subclassify these patients according to the behavior type. Two were hebephrenic; 2 were catatonic; 1 was paranoid, and 1 was manic. All the patients had excitement states. The results of treatment with diphenylhydantoin were variable and not distinctly convincing in 5 patients. However, an excellent result was obtained with the manic patient, whose case will be presented in detail.

CASE 3.—The now 45 year old white woman, M. T., was admitted to the Delaware State Hospital on Oct. 8, 1937. The family history revealed several cases of alcoholism and mental deficiency. The patient was always restless but became especially irritable during the menstrual period. She became increasingly restless and talked continuously but was kept at home as long as the family was able to supervise her. After the death of the mother, however, she became actually disturbed, refused to go to bed at night and kept the family awake through constant talking. On admission she appeared agitated, elated, untidy and assaultive and had to be put in a ward for disturbed patients. She became somewhat more cooperative during the years after her admission, but she remained restless and noisy. She was unable to sit still, rocked back and forth, talked in a rambling fashion and produced screaming or barking noises in a staccato fashion.

Treatment with diphenylhydantoin was started with 4 capsules daily, and the dose was increased to 6 capsules within three days. A steady decrease of restlessness and noisiness was observed, and within a week the patient appeared more controlled than at any time prior to the treatment. On the twenty-second day of the treatment a generalized macular exanthem developed, and she complained of pruritus. The temperature and the blood count remained normal. Administration of diphenylhydantoin was discontinued, and the skin cleared in a few days. The improvement in behavior did not last for more than three to four days after the drug was discontinued. A second course of treatment with diphenylhydantoin was started after three months, but the daily maintenance dose was reduced to 4 capsules. Again, she responded favorably, as restlessness and noisiness disappeared within ten days. She still talked to herself and remained somewhat elated and flighty, but she was not disturbed. Medication was discontinued after twenty-six days because she complained of dizziness and itching sensations. A third course of treatments was again successful but had to be discontinued after three weeks, as she again complained of dizziness and became ataxic. Improvement of behavior never lasted longer than a few days after medication was discontinued. Except for her apparent idiosyncrasy to diphenylhydantoin, the patient responded most favorably to the treatment. This result was undoubtedly due to the specific action of the drug, since she had not shown similar improvement either spontaneously or with other treatments.

Organic Psychosis.—Three patients with an organic type of psychosis, 2 with dementia paralytica and 1 with a postencephalitic behavior disorder were included in this investigation because they showed pronounced psychomotor disturbances. One of the patients with dementia paralytica, who was generally deteriorated, went through phases of manic excitement. No definite improvement was observed during treatment with diphenylhydantoin. The other patient with dementia paralytica was rather dull and listless but had frequent spells of excitement and screaming, which seemed to represent reactions to hallucinations. Diphenylhydantoin did not improve this condition. The patient with a postencephalitis disturbance was given the drug because of the unsatisfactory results with scopolamine and other related drugs. Diphenylhydantoin sodium was administered alone and in addition to scopolamine. No improvement occurred with either type of medication.

COMMENT

Kalinowsky and Putnam concluded that diphenylhydantoin sodium has an effect on disturbances of mood, not only in epilepsy but in various other types of psychoses, and they expressed the belief that this fact contributes to the accumulating evidence of a chemical concept of both epilepsy and the major psychoses. The organic concept of these psychoses has been supported by various recent electroencephalographic studies. It would have been desirable to study the electroencephalographic patterns of the patients prior to, during and after treatment with diphenylhydantoin in order to gain a more objective knowledge of the cerebral dysfunction and of the influence of this drug on abnormal electroencephalographic rhythm. It appeared, however, most difficult to find a practical solution to the problem of obtaining reliable records from disturbed and uncooperative patients. Some essential facts about the specific action of diphenylhydantoin were determined by correlating psychopathologic phenomena with positive and negative reactions to the drug. It was emphasized earlier in this report that a merely statistical evaluation of the results of this study would be misleading because it would not do justice to the striking differences in psychopathologic symptoms. From a quantitative viewpoint, only a small number of patients showed favorable results. A qualitative analysis of the cases, however, seems to indicate that a certain type of patient reacts in a specific fashion to diphenylhydantoin. The advantage of the one year period of observation was twofold: Spontaneous remissions were excluded by a repetition of the course of treatments, and an intimate knowledge of the individual symptoms of every patient was gained. This knowledge of the behavior patterns of the patients provided the basis for a more thorough understanding of the nature of the excitement states. It soon became evident that the action of diphenylhydantoin on states of excitement is not symptomatic per se but depends on the nature of the excitement state. Only excitement states which seemed to be caused by the fundamental factors of the psychosis reacted to the drug, whereas states of excitement representing reactions to secondary, i. e., psychogenetic, factors remained uninfluenced. It is not overlooked that reactions of the second type are psychopathologic phenomena, expressing a particular person's way of adjustment to a certain situation. The excitement of the first type, however, seems to be caused by a more fundamental, i. e., pathophysiologic, disturbance. One is led to believe that states which react favorably to diphenylhydantoin belong exclusively to this type. This observation gives support to the concept of the "fundamental disturbance" in the psychoses which was introduced by a number of authors, notably, Bleuler,[4] Birnbaum[5] and Küppers.[6] Further objective evidence in this direction can be found in electroencephalographic studies of Finley,[7] who succeeded in obtaining tracings during and between psychotic episodes. He reported, for instance, a case of catatonic excitement in which rapid frequency occurred during a state of emotional turmoil and decreased notably when the condition was in remission.

Interesting observations were made with intravenous injections of sodium amytal. Patients with excitement states of the primary type showed no significant change in talk or behavior while under the influence of sodium amytal, but patients whose excitement states were reactions to psychogenic factors often appeared considerably relaxed and more responsive. This observation supports the belief that in treatment with diphenylhydantoin the hypnotic action can be disregarded.

Electric shock therapy did not seem to be favorably influenced by previous treatment with diphenylhydantoin. Kalinowsky and Putnam reported that subsequent electric shock treatments in several instances led to a remission after only one convulsion, and they planned systematic attempts at medication with diphenylhydantoin prior to shock treatment. According to experience with patients selected for this investigation, previous treatment with diphenylhydantoin rendered the patient more resistive, and duration of shock and voltage often had to be increased. The number of convulsions needed before improvement took place was not decreased and varied greatly.

If one observes psychotic patients daily for a year, one cannot fail to notice that many types of favorable changes occur spontaneously, and one becomes progressively immune to therapeutic positivism. Many cases, thought to be therapeutic successes, were disregarded because the patients showed equally favorable reactions during the intervals between treatments. On the

4. Bleuler, E.: The Physiogenic and Psychogenic in Schizophrenia, Am. J. Psychiat. **10**:203, 1930.

5. Birnbaum, K.: Kriminal-Psychopathologie, Berlin, Julius Springer, 1921.

6. Küppers, E.: Ueber den Begriff der Grundstörung und seine Bedeutung für die Einteilung und die Lokaldiganose der Geisteskrankheiten, Arch. f. Psychiat. **99**:1, 1933.

7. Finley, K. H.: On the Occurrence of Rapid Frequency Potential Changes in the Human Electroencephalogram, Am. J. Psychiat. **101**:194, 1944.

other hand, greater significance could be attributed to the cases in which the reaction could be considered positive after all coincidental facors had been eliminated, because here it was certain that diphenylhydantoin exerted a specific influence.

In his discussion on the paper in which he reported diphenylhydantoin sodium to be an effective anticonvulsant, Putnam [8] stressed the fact that there were several kinds of convulsions and suggested that there should be several types of medication to control them. It now seems that there are different kinds of nonepileptic psychomotor excitement states, some of which are caused by pathophysiologic disturbances and can be controlled with diphenylhydantoin. Further studies on the usefulness of this drug for these specified psychotic states promise to contribute to the chemical treatment of the psychoses, as well as to the further clarification of an organic concept of the major psychoses.

8. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1073 (Sept. 17) 1938.

The diphenylhydantoin sodium was supplied by Parke, Davis & Company, Detroit.

Delaware State Hospital.

THE HUMAN PYRAMIDAL TRACT

XI. CORRELATION OF THE BABINSKI SIGN AND THE PYRAMIDAL SYNDROME

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The present study is an attempt to correlate the symptoms and signs of the pyramidal tract syndrome with the Babinski reflex. A destructive upper motor neuron lesion involving the pyramidal bundle has been said traditionally to produce the following abnormalities: paralysis of the spastic type; hyperactive tendon reflexes; loss of the superficial abdominal and cremasteric reflexes; appearance of certain pathologic reflexes among which is the extensor toe sign of Babinski, and, finally, absence of the reaction of degeneration in the peripheral nerves. Paralysis, the most important feature of the syndrome, is defined as loss of the power of movement. Evidence is accumulating that the Babinski sign can be elicited by general suppression or inhibition of somatic nerve activity. If the pyramidal tract is entirely involved in the mechanism of production of this extensor toe sign, one can be more specific and say that possibly a physiologic block of nervous energy in the tract is the causative factor. For example, the Babinski reflex can be produced in deep sleep; it can be elicited during a certain stage in the pharmacologic action of such drugs as pentobarbital sodium and scopolamine; prolonged physical exertion predisposes to its appearance; the reflex is present in hypoglycemic shock, it exists potentially in cases of loss of blood in certain quantities from injured vessels, which may be located remote from the site of the central nervous system, and the indications are that a temporary sign may be produced on proper stimulation in some systemic and neurologic diseases. The voluntary striated muscles in many of these situations are merely in a state of flaccid quiescence; and if the causative factor is remedied in time, the extensor toe sign reverts to the normal flexor type, with no residuum of motor deficit. If suppression, as well as destruction, of somatic neurons in the central nervous system is a possible factor in the production of the Babinski reflex in some disease processes affecting the central nervous system, then variable voluntary motor deficits might be expected to occur. The literature has been canvassed for reports of cases in which the Babinski sign was exhibited, in an attempt primarily to test the validity of this assumption.

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This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

MATERIALS AND METHODS

Reports of 1,600 individual cases of the pyramidal tract syndrome in each of which either a unilateral or a bilateral Babinski sign was exhibited were collected from the ARCHIVES, the *Journal of Nervous and Mental Disease* and *Brain*. This sign has been correlated with the reported age and sex; the laterality; the somatic motor deficit; the state of tone of the muscles, and the activity of the tendon, abdominal and cremasteric reflexes.

RESULTS

In 1,008 of the 1,600 cases the condition was chronic; in 480, it was acute, and in 112 cases it could not be classified. The chronicity was determined on the basis of the onset of motor deficit rather than of any other feature of the disease process, whatever it may have been.

In 915 cases the patients were males, in 624 cases, females, and in 61 cases the sex was not mentioned. Thus the ratio of males to females was 1.5 to 1.

In 216 cases the patients were between 1 and 10 years of age; in 232 cases, between 11 and 20; in 231 cases, between 21 and 30; in 278 cases, between 31 and 40; in 297 cases, between 41 and 50; in 215 cases, between 51 and 60; in 93 cases, between 61 and 70, and in 18 cases, between 71 and 80. No case fell in the age group of 81 to 90 years; 1 was in the group of 91 to 100 and, finally, in 19 cases the age was not given.

In 905 cases the Babinski reflex was bilateral; in 682 cases it was unilateral, and in 13 cases no information as to the laterality was given. Thus the ratio of bilateral to unilateral recurrence was 1.3 to 1. Of the 1,600 cases, the Oppenheim reflex was reported to be present in 83; the Chaddock sign, in 65; the Hoffmann

sign, in 57; the Gordon sign, in 34; the Rossolimo sign, in 31; the Mendel-Bechterew sign, in 18, and the Schäffer sign, in 6, a total of 294 cases.

In 984 cases the knee jerk was reported as hyperactive; in 209 cases, as hypoactive, and in 32 cases, as normal, whereas in 375 cases it was not mentioned.

Ankle clonus was described as present in 400 cases, and the patellar clonus, in 70 cases.

Spasticity occurred in 548 cases, whereas flaccidity was characteristic in 87 cases.

Absence of abdominal reflexes was reported in 628 cases and absence of the cremasteric reflexes in 96 cases.

According to the descriptions, every degree of paralysis, when present, from slight to complete loss of the power of movement, goes hand in hand with the Babinski sign. In 51 cases the observers stated that they could not detect any somatic motor deficit on examination. In the great majority of cases, however, some degree of motor loss was present. In a number of cases the deficiency was confined to certain of the cranial muscles. Then, again, only muscles in the arm, or combinations of muscles of the head and arm, were paralyzed. In the lower extremities, voluntary motor deficit was classified by clinical investigators according to diminished strength in the muscles, to abnormalities in gait or to impaired movement. In some cases scientific terms were employed to designate loss of power of movement, such as hemiplegia, hemiparesis, paraplegia, paresis, palsy, tetraplegia or monoplegia, but such instances were in the minority.

Strength in the muscles was expressed by such terms as feebleness, weakness, impaired power, diminished power, weakness but no evident paralysis, fairly well preserved power, well preserved motor power and loss of power. Some of the terms used to express faulty gaits were dragging of the foot, inability to stand and walk, staggering, shuffling, unsteadiness, stumbling, slowness, sluggishness, limping, straddling and lameness. Expressions used to describe movement were motionlessness, slowness, awkwardness, clumsiness, feebleness and well preserved and limited movement.

Because there is evidence that suppression of nerve activity in the pyramidal tract alone or in combination with other tracts may be responsible for a potential Babinski sign, 199 cases were collected in which inhibition of somatic nerve activity was a possible factor. The disturbance was clinically classified as sleep, unconsciousness, coma, stupor, drowsiness and somnolence. In all (100 per cent) of 6 cases in which the patient was described as being in a state of sleep a bilateral Babinski sign was present. Corresponding values for the other states were as follows: unconsciousness, 35 of 39 cases (89.7 per cent); coma, 55 of 63 cases (87.3 per cent); stupor, 28 of 33 cases (84.8 per cent; drowsiness, 37 of 48 cases (77.0 per cent), and somnolence, 7 of 10 cases (70 per cent). The values for the entire series showed that in 168 of 199 cases, or 84.4 per cent, a bilateral Babinski sign was exhibited.

COMMENT

From the descriptions given in the reports of 1,600 cases with the Babinski sign, it is apparent that this reflex can be elicited in disease conditions in which the state of the voluntary striated muscles is judged to vary from normal to complete paralysis. In the majority of the cases there was some form of motor deficit, which, however, did not always involve the lower extremities. The motor loss was judged in terms of strength in the muscles, the appearance of the gait or the power of movement.

The seven pathologic reflexes other than the Babinski sign played an insignificant quantitative role in the 1,600 cases studied. Collectively, they were reported in only 294 cases (19.6 per cent).

The various pyramidal signs and symptoms which were reported can be graded with respect to their frequency in the following order: somatic motor deficit, 1,376 cases; hyperactive patellar reflex, 984 cases, absence of superficial abdominal reflexes, 628 cases; spasticity, 548 cases; ankle clonus, 400 cases; hypoactive knee jerk, 209 cases; absence of cremasteric reflexes, 96 cases; flaccidity, 87 cases, and patellar clonus, 70 cases.

In this series, the ratio of male to females involved was 1.5 to 1. Whether this distribution means that the motor system of the male is more susceptible to attack than that of the female is speculative.

Cases of the chronic type were more numerous than those of the acute form, the proportion being 2.1 to 1. The chronicity was determined for the series by the onset of motor difficulties. Thus, in all cases in which there was evidence of motor deficit of more than two months' duration the condition was classified as chronic.

The age factor in the series showed involvement in about an equal number of cases in each of the first six decades of life, and then there occurred a sharp fall between the seventh and

the tenth decade. The greatest actual number of cases was in the age groups of 41 to 50 years. One might expect the Babinski sign to be more prevalent in elderly persons, but it may be that not as many patients in the advanced age groups were examined.

An interesting feature of the study was the evaluation of the Babinski sign in cases in which unconsciousness, coma, stupor, sleep, drowsiness or somnolence was reported. These conditions clinically seem to simulate the states produced by hypoglycemic shock, loss of blood or the pharmacologic action of such drugs as pentobarbital, in which the Babinski sign can be elicited. In these neurologically suppressed conditions, a bilateral Babinski sign was common, occurring in 84.4 per cent of cases. In the entire series of 1,600 cases studied, the ratio of the incidence of a bilateral to that of a unilateral Babinski sign was 1.3 to 1. For the series of cases of coma, etc., the ratio was 5.4 to 1. The degree of general inhibition of nerve activity may be important, therefore, in the mechanism of the Babinski sign. It is possible that this reflex might have been elicited in 100 per cent of such cases had the attempt been made at a critical stage in the inhibitory process. The question arises: If general reduction of activity of the central nervous system can produce a state in which the Babinski sign may be elicited on stroking the outer portion of the sole, would local inhibition of the pyramidal tract without destruction do likewise? If the pyramidal bundle is concerned at all with the Babinski sign, I believe the latter may be a distinct possibility.

It is realized that the many clinicians who were involved in the present study did not select the majority of their cases for the purpose of investigating the pyramidal tract syndrome. The Babinski sign has been singled out in the literature in the form of individual cases and correlated with the signs and symptoms long regarded as being due to destruction of the pyramidal tract. Within the limits of the survey, there is an indication that the Babinski reflex goes hand in hand with all shades of muscular activity, from that judged to be normal to complete paralysis. Also, it is possible that an inhibitory factor may play a role in the mechanism of the Babinski reflex. In the absence of any extended investigations limited directly to the problem, it is believed that the over-all results of the study may indicate the true status of the Babinski sign in clinical medicine.

CONCLUSIONS

The results of a correlation study of 1,600 individual cases of the pyramidal tract syndrome in which the Babinski sign was exhibited may be summarized as follows:

1. The ratio of male to females was 1.5 to 1.

2. The Babinski sign occurred most frequently in the age group between 41 and 50 years and rapidly diminished in frequency after the sixth decade of life.

3. The proportion of cases of the bilateral Babinski sign to cases of the unilateral sign was 1.3 to 1.

4. Of about 200 selected cases in which were exhibited various degrees of general suppression of somatic nerve activity, such as that which occurs in sleep, unconsciousness, coma, stupor, drowsiness and somnolence, the Babinski sign was bilateral in about 85 per cent. The ratio of cases of the bilateral to cases of the unilateral Babinski sign in this group was 5.4 to 1.

5. All degrees of muscular activity, from the normal to complete paralysis, were judged to be present with the Babinski sign.

6. The signs and symptoms, in the order of their frequency, were as follows: somatic motor deficit, hyperactive patellar reflex, absence of superficial abdominal reflexes, spasticity, ankle clonus, hypoactive knee jerk, absence of cremasteric reflex, flaccidity and patellar clonus.

7. The criteria used to describe somatic motor deficit in the lower extremity were strength in the muscle groups, faultiness in gait and loss of power of movement.

8. Such pathologic reflexes as the Oppenheim, Chaddock, Hoffmann, Gordon, Rossolimo, Mendel-Bechterew and Schäffer signs played an insignificant quantitative role in the cases studied.

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PRIMITIVE HABITS AND PERCEPTUAL ALTERATIONS IN THE TERMINAL STAGE OF SCHIZOPHRENIA

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In the last decade the main interest in the study of schizophrenia has been concentrated on cases of the early stage of this illness, which are the most suitable for dynamic psychologic investigations and in which a better response to the newly devised shock treatments is obtained. The study of cases of chronic schizophrenia has, on the other hand, been rather neglected except for statistical purposes. I am in accord with the numerous other workers who think that even the study of patients in the most advanced stages of this illness may eventually reveal important information on the nature of this condition. This point of view led to the present investigation of peculiar habits and of quasineurologic (or neurologic?) phenomena noted in the terminal stages of dementia precox. The word habit is employed here for want of a better term. It is used to mean a certain type of behavior intermediate between reflexes and voluntary acts but always definitely reactive in nature.' Goldstein's [1] term "performance" could be used except for the fact that the behavior discussed here is a special kind of performance, being spontaneous and habitual. The term "automatic act" is also discarded because by this term is often meant an act which has become such through repetition or training. The study on the coprophagic habit has already been reported.[2] The habit of "placing into mouth" has also been discussed [2] but will be reconsidered here in relation to broader implications. The phenomenon of negativism will not be included in this report because it is not found exclusively in the terminal stage of dementia precox but is more characteristic of less advanced stages. Other habits which belong to preterminal stages of dementia precox will be discussed in later contributions.

This study was carried out on 250 female patients with the chronic form of schizophrenia who had been hospitalized in institutions for mental disease from seven to forty-seven years.

OBSERVATIONS

It is well known to all observers that decreased activity is one of the most common, though not a constant, characteristic of progressing schizophrenia. This motor reduction often interferes with the dietary requirements of the patient to such a point as to bring about a state of malnutrition, anemia and, occasionally, avitaminosis. This inactivity, which is a part of the psychic isolation of schizophrenia, is noted throughout the long years of progressing regression, interrupted only by occasional and transitory partial remissions. In patients, however, who continue to regress indefinitely, a more or less sudden increase in motor activity is noted at a certain moment. As a rule such an increase is not transitory but lasts for the lifetime of the patient, or until a physical illness neutralizes its effects. It is when this partial increase of motor activity takes place that what I call the terminal stage of dementia precox begins. In the patients whom I observed and whose clinical records I studied, such a stage started any time from seven to forty years after the onset of the illness, but it probably may start even sooner, or later. This increase in activity is only relative, since the patients remain somehow underactive in comparison with normal subjects. Their actions, which are now more numerous, appear sharply reactive or impulsive: They are reactive to certain habitual situations, which will be taken in consideration shortly, or impulsive, inasmuch as they appear to be due to sudden internal stimulation. The patients may be impulsively destructive, assaultive and much more violent than previously. At this stage of the illness they do not seem able any longer to experience hallucinations or to elaborate delusions, although it may be that since they are no longer capable of expressing themselves verbally, such symptoms cannot be elicited. In fact, their verbal expressions are either completely absent or reduced to a few disconnected utterances.

The most striking changes, however, are noted in the dining room. The patients who had

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1. Goldstein, K.: The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man, New York, American Book Company, 1939.

2. Arieti, S.: The "Placing-into-Mouth" and Coprophagic Habits, Studied from a Point of View of Comparative Developmental Psychology, J. Nerv. & Ment. Dis. **99**:959 (June) 1944.

always eaten so little as to have reduced themselves to a state of malnutrition now seem to have a voracious appetite (bulimia) and often gain a considerable amount of weight. The nurses often report that these patients have the habit of stealing food. In reality, closer observation reveals that the concept of stealing is not implied in the actions of these patients. They cannot prevent themselves from grabbing food at the sight of it, so that they are better termed food grabbers. Observations in the dining room reveal other interesting habits. A few of these patients show preference for certain foods. No matter how many kinds of food are in their dish, they always grasp first and eat the preferred food. They do not alternate the various kinds, as normal adults do, but only when they have entirely finished the preferred food do they start to eat the others. Similarly, if they show several degrees of preference, they first eat the food which is the first choice; when this is finished, they eat the second choice, and so on. If there are desserts, they are generally eaten before anything else. It seems that the patients are obliged to react first to stronger stimuli. The preference for a certain food is not shown by all patients who are food grabbers. On the other hand, such preference is maintained only for a brief period after the acquisition of the food-grabbing habit. After this period the patients seem to eat with avidity any kind of food. Whatever belongs to the category of edibility is equally and promptly reacted to. Another characteristic which is often observed is the extreme rapidity with which these patients eat (tachyphagia). In a few minutes these food grabbers may finish the rations of several patients, if not prevented. Often they do not leave in the dish any remnant of food but clean the plate with their tongue.

The patients may remain indefinitely at this stage characterized by the food-grabbing habit, but the majority progress more or less rapidly to a more advanced stage, characterized chiefly by what I have termed the habit of "placing into mouth." At this stage the category of edibility is no longer respected. Whereas the patients had previously distinguished themselves for grabbing food and food only, now they manifest the habit of grabbing every small object and putting it into the mouth, paying no attention at all to the edible or nonedible nature of it. If not prevented, these patients pick up from the floor crumbs, cockroaches, stones, rags, paper, wood, clothes, pencils and leaves and put them into the mouth. Generally they eat these things; occasionally they swallow them, with great risk. Many patients, however, limit themselves to chewing these nonedible objects and finally reject them. When they eat or swallow dangerous materials, such as an ink well or a teaspoon, they are erroneously considered as suicidal. Closer observation reveals, however, that the idea of suicide is not implied in their action. They simply react to a visual stimulus by grasping the object and putting it into the mouth. They act as if they were coerced to react in this way. It is as though they were especially attracted by small three dimensional stimuli, which seem to be distinguished more distinctly than usual from the background.

The patient may remain indefinitely at this stage, but some of them progress to a more advanced phase, which is characterized by apparent sensory alterations. On account of the lack of cooperation and communicability of these patients, such alterations cannot be studied with the usual neurologic technic, but much stronger stimuli, not ordinarily used, or observation of the patient's reactions in certain special situations must be employed. Therefore only gross alterations are reported here, and no claim to accuracy is made.

It seems as though the patients who have reached this stage are insensitive to pain. They appear analgesic not only to pinprick but to much more painful stimuli. When they are in need of surgical intervention and have to have sutures in such sensitive regions as the lips, face, skull or hands, they act as though they could not feel anything, even in the absence of any anesthetic procedure. I have many times sutured wounds caused by their violent and assaultive behavior without eliciting any sign of pain or resistance. Other patients seem to feel some pain, but far less than normal persons would. Only exceptionally is there a local withdrawal. The same anesthesia is noted for temperature. The patient may hold in his hands a piece of ice without showing any reaction. Pieces of ice may also be placed over the breast, abdomen or other sensitive regions without eliciting any reaction or defensive movement. Such patients also appear insensitive when the flame of a candle is passed rapidly over the skin. They may sit near the radiator, and if they are not removed, they may continue to stay there even when, as a result of close contact, they are burned. This state of insensitivity is in my opinion one of the chief causes of the large number of burns occurring in wards in which deteriorated schizophrenic patients live.

One may be induced to interpret this lack of responsiveness to pain and temperature stimuli not as true anesthesia but as an expression either of catatonic inactivity or of a certain kind of "inner negativism." Repeated observations have,

however, led me to the conclusion that such an interpretation is not valid. The patients who show anesthesia for pain or temperature stimuli are not as a rule inactive; on the other hand, they show the aforementioned relative increase in activity which, together with the apparent anesthesia, is responsible for numerous accidents. The possibility that these patients do not react to dangerous sensations on account of inner negativism is, in my opinion, also untenable because many such patients do not show other signs of negativism. As I have already mentioned, the phenomenon of negativism, although not absent at this stage of the illness, is much more commonly observed in patients who have reached a less advanced stage. On the other hand, the possibility that pain and temperature sensations are perceived, but that only the affective components of such perceptions are lost, must be taken into consideration and will be discussed later. In a small number of patients this apparent anesthesia or hypesthesia for pain and temperature stimuli is only transitory. Even patients who have been insensitive to heat for several months may to some extent reacquire capacity to perceive pain or temperature sensations or both. Occasionally striking changes occur at brief intervals. However, I have the impression that some degree of hypesthesia is always retained. Partial hypesthesia is also found in many patients who have not yet reached what is here called the terminal stage. Tactile perception does not seem impaired in these patients. Tendon and superficial reflexes are not only present but often increased. The corneal reflexes are also present. On the other hand, many, but not all of the patients who present anesthesia for pain and temperature stimuli seem also to have lost the sensation of taste. When they are given bitter radishes or teaspoons of sugar, salt, pepper or quinine, they do not show any pleasant or unpleasant reaction. They do not spit out the unpleasant substances as quickly as possible, as do control mentally defective persons or deteriorated patients with organic disease, but continue to eat the entire dose without hesitation. Some of them seem to recognize salt but do not object to pepper or quinine. Others react mildly to quinine but not to pepper or salt.

In contrast to this lack of reactivity to pain, temperature and taste stimuli is the normal reaction to strong olfactory stimuli. Patients who did not react at all to such stimuli as flames, pieces of ice and suturing react in a normal way when they smell such things as ammonia and strong vinegar. They withdraw quickly from the stimulus, with manifest displeasure. Such a reaction strikes the observer, inasmuch as many other strong stimuli from other sensory fields do not bring about any response, or only a mild reaction. It seems as though the phylogenetically ancient olfactory sense could better resist the schizophrenic process. However, the schizophrenic patient does not seem to make use of these olfactory sensations as he could, probably on account of that lack of initiative which more or less characterizes the entire course of his illness.

The aforementioned phases of the terminal stage of dementia precox (phases characterized by the food-grabbing habit, the "placing into mouth" habit and apparent anesthesia for pain, temperature and taste sensations and preponderance of the olfactory sense, respectively) do not always occur in the order given. A large number of patients, especially, but not exclusively, those of the paranoid type, remain indefinitely at a less advanced stage. In others two stages of the illness overlap. For instance, a few patients who have the food-grabbing habit may retain the capacity to hallucinate. Other food grabbers may already have anesthesia for pain and temperature stimuli, and so on. However, the order described is the one in which I have most commonly observed appearance of the symptoms. Occasionally a patient may improve and return to a less advanced stage. Intravenous injections of sodium amytal do not produce any perceptible change in the picture of the terminal stage of schizophrenia.

Although statistical conclusions are premature and difficult on account of this overlapping of symptoms, I have the impression that the number of patients presenting the habit of grabbing food or of placing objects in the mouth is large in services for patients with chronic mental disease. The number of patients presenting some hypesthesia for pain, temperature and taste sensations is also large. On the contrary, patients presenting absolute anesthesia for pain and temperature sensations are relatively few.

INTERPRETATION

A genetic approach may help in explaining some of the habits described. In fact, it is possible to interpret them not as newly acquired habits but as behavior manifestations of lower levels of integration.

The food-grabbing habit reminds one of what is generally observed in cats, dogs, monkeys and other animals. The animal is coerced to react to the food, at the sight of it. The food does not stand for itself but is what Werner[3] calls

3. Werner, H.: Comparative Psychology of Mental Development, New York, Harper & Brothers, 1940.

a "thing of action." It is a "signal thing," the sight of which leads immediately to a fixed action (Werner [3]). The animal cannot delay the reaction or channel the impulse into longer integrative circuits. Similarly, others of the habits previously described disclosed the same syncretic characteristics encountered in more primitive organizations. It is well known that when monkeys, dogs, cats and other animals are given at the same time different items of food, they eat first the preferred food (for instance, meat in case of the dog, or banana in case of monkeys), and only when the entire portion of the preferred food is finished do they start to eat the other foods. They cannot alternate the various kinds but are coerced to react first to the strongest stimulus. Also, a 3½ to 4 year old child, if not prevented, eats first the preferred food, and only when he has finished it does he eat the others.

When the patients become even sicker, this integration of the stimuli is even more primitive, so that they react to edible and nonedible objects in the same way by grasping them and putting them into the mouth. The category of edibility is no longer respected. This "placing into mouth" habit was discussed in a previous report.[2] It was there emphasized that a similar behavior is noted in children approximately 1 to 2 years of age. The similarity of this behavior to that observed by Klüver and Bucy [4] in monkeys which underwent removal of both temporal lobes was also discussed. There is one chief difference, however: Whereas the monkeys are described as smelling the grasped object before placing it into the mouth, children and deteriorated schizophrenic patients do not smell the object but put it immediately into the mouth. However, if the olfactory tracts of the monkeys were cut previous to removing both temporal lobes, no smelling was observed. Klüver and Bucy considered the monkeys with both temporal lobes removed as psychically blind (being unable to recognize the edible or nonedible nature of the objects in spite of the fact that they were trained before the operation to make this differentiation). I am inclined to consider the "placing into mouth" habit in deteriorated schizophrenic patients as a primitive response in the mechanism of which a short-circuiting takes place between the functions of reception and those of reaction, with exclusion of usual normal paths which involve higher centers. It may be that instead of the normal path a circuit is used similar to that involved in the relatively primitive physiologic complex which Edinger [5] called "oral sense." As happens in all other short-circuit reactions, an impulse or coercion to react, and not asymbolia, may be responsible for the "placing into mouth" habit. Klüver and Bucy considered as hopeless any attempt to reduce to one basic defect the polysymptomatic picture presented by their monkeys with bitemporal lobectomy. Although any comparison is hypothetic, it may be that these monkeys have this oral habit because after the surgical operation they are coerced to react to tridemensional visual stimuli and have to use short circuits. This consideration, however, does not deny the possibility that these monkeys are, at least partially, psychically blind. On the other hand, they probably are psychically blind, as considerations to be discussed later will indicate. The same inability to distinguish between edible and nonedible objects was also noted by Langworthy [6] in cats which underwent removal of both frontal poles. The tendency to grasp every object and to put it into the mouth was also reported by von Braunmühl and Leonhard [7] in cases of Pick's disease. It may be of some importance to mention also that I have noted the sudden occurrence of bulimia, tachyphagia and the "placing in mouth" habit after bilateral prefrontal lobectomy in a catatonic patient who had been sick for more than ten years.

The analgesia observed in some of the deteriorated patients may now be considered. Several authors have reported altered perception of pain in cases of early catatonia, and Bender and Schilder [8] discussed this subject in relation to the capacity to acquire conditioned reflexes. In my experience the hypesthesia found in patients with early catatonia is generally not so severe as that observed in patients who have reached the terminal stage, and often is not detected if, instead of pinprick, one uses stronger stimuli. Anesthesia for temperature and taste

4. Klüver, H., and Bucy, P. C.: (*a*) "Psychic Blindness" and Other Symptoms Following Bilateral Temporal Lobectomy in Rhesus Monkeys, Am. J. Physiol. **119**:352 (June) 1937; (*b*) An Analysis of Certain Effects of Bilateral Temporal Lobectomy in the Rhesus Monkey, with Special Reference to "Psychic Blindness," J. Psychol. **5**:33, 1938; (*c*) Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, Arch. Neurol. & Psychiat. **42**:972 (Dec.) 1939.

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stimuli is even more rare in patients with early catatonia and is not comparable to that encountered in my patients, with conditions originally diagnosed as various types of dementia precox. However, the possibility is not denied that the nature of the phenomenon may be the same. In many of the common textbooks on psychiatry no mention is made of this analgesia encountered in some deteriorated schizophrenic patients. Bleuler,[9] however, described this phenomenon as follows:

> Worthy of note is an analgesia which occurs in schizophrenia not too rarely and which is sometimes quite complete. It is responsible for the fact that the patients readily injure themselves purposely or accidentally.

In agreement with the observations of Bender and Schilder on patients with early catatonia, I am inclined to believe that the real sensation of pain and temperature is not lost in my patients. The fact that the corneal reflexes are always retained may be a proof of it. However, these patients seem to be unaware of the painful and thermic stimuli and do not show any emotional reaction to them. They seem to be unable to perceive the stimuli. In other words, the rough sensation may be present but remains isolated and is not elaborated to the perception level. The patients are unable to recognize the emotional and cognitive value of the thermic and painful stimuli and therefore are unaware of the possible dangers which they at times imply. That is the reason that they often hurt themselves. These patients for all practical purposes have agnosia and may be compared to persons with sensorial aphasia who hear a spoken language without understanding it.

Is this loss of nociceptive perception only an exaggeration of the general schizophrenic emotional indifference? Probably the cause of these psychophysiologic derangements is the same, but for all practical purposes these patients are better described as having agnosia and may be termed "psychically analgesic," and not apathetic only. They fail to perceive pain and temperature sensation, not only from an emotional but from a cognitive point of view. That is the reason that they so often hurt themselves if they are not under constant supervision. The problem whether these phenomena are due to loss of emotional capacity or to loss of perception of pain and temperature sensation is probably only academic at present, when so little is known about emotivity and its relation to perception of pleasant and painful sensations. Herrick,[10] who took into consideration this relation, stated: "Pain, considered psychologically and neurologically, is a sensation, and a different neurological mechanism for unpleasantness and pleasantness must be sought." Pain, however, is in normal conditions always associated with unpleasantness. In the patients described it is not. The relation between emotional indifference and agnosia has also been taken into consideration by von Monakow and Mourgue,[11] who observed impairment of emotions in aphasic persons. In other publications[12] the same authors considered the possibility that asymbolia may be due to disturbances in the affective sphere.

The fact that taste perception is often lost or impaired in these analgesic patients and that the olfactory perceptions are preserved instead is also thought stimulating. The association of taste and pain asymbolias points to the conclusion that taste should be included among the general somatic sensations, as investigations by the school of Fulton[13] and by Shenkin and Lewey[14] seem to prove. The striking survival of smell perceptions, which are phylogenetically very old, may induce one to think that the archipallium is more resistant than the neopallium to the schizophrenic process. The olfactory sense, which is the dominant sense in lower vertebrates, seems to reacquire in some deteriorated schizophrenic patients a position of predominance among the senses, not because of increased acuity but because of impairment of perceptions of stimuli coming from other sensory

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fields. However, contrary to what is found in lower vertebrates, these schizophrenic patients do not take advantage of the olfactory sense as they could, possibly on account of their general volitional impairment or general withdrawal. It is interesting to observe that the sense of smell in schizophrenic patients is not involved even in short-circuiting reactions, whereas it was involved in the monkeys of Klüver and Bucy. The fact that perception and emotional reactions connected with the sense of smell are not impaired in many patients in the terminal phases of schizophrenia may be due instead to the peculiarity that the olfactory stimuli are the only sensory stimuli which do not pass up to the thalamus.

The last consideration may induce one to examine the possibility of anatomic interpretations of the symptoms described. Any interpretation of this kind has of course to be considered preliminary at the present time, when so much remains to be learned about the schizophrenic process. Furthermore, any deduction concerning human beings made from experimental observations on animals may be advanced only in a hypothetic way.

If, on the basis of reported observations, one were to localize an alleged pathologic process responsible for the release of the primitive habits previously described, one would probably have to incriminate the prefrontal lobes (Langworthy) and the temporal lobes, (Klüver and Bucy, von Braunmühl and Leonhard), and the lesions would have to be bilateral and presumably symmetric. The problem of localizing the process responsible for the analgesia is even more difficult, after the work of Head, although there is again much evidence that the parietal lobes are the site of sensation and perception of pain. Schilder and Stengel [15] found asymbolia for pain in cases of lesions of the gyrus supramarginalis; Bender and Schilder expressed the belief that it is impossible to deny the presence of a dysfunction of the same areas in catatonic patients presenting pain asymbolia. Patterson and Stengel [16] reported "apperceptive blindness" and asymbolia for pain in a case of Lissauer's dementia paralytica in which lesions in the parastriatal areas were present. Since in my patients pain asymbolia is often associated with taste asymbolia, or "psychic ageusia," it may be that the perceptual centers for taste and pain are located near each other. It has already been mentioned that recent investigations seem to confirm a parietal localization of the taste centers.[17] These anatomic considerations are not solidly founded. However, one deduction has a certain probability of being correct. If, on the basis of the reported observations, one were to localize an alleged pathologic process responsible for the symptoms occurring in the terminal stage of schizophrenia, one would have to place it in the so-called silent areas, or great association areas, and not in the recognized primary cortical centers. These areas would, also, be approximately those which, according to the investigations of Flechsig [18] and Vogt,[19] are the last to myelinate and the last to appear phylogenetically. Bilateral impairment of these great association areas would make impossible those "long-circuiting processes" mentioned by Fulton [20] and reemphasized by Cobb,[21] and would be responsible for the occurrence of short-circuit processes manifesting themselves as primitive habits.

The theories of Orton [22] seem also confirmed by my observations. According to this author, three levels of cortical elaborations may be distinguished.[22a] The first elaborative level, consisting of the so-called projection areas, or the arrival platform cortex, is the first to receive stimuli of external origin. The second level, consisting of the areas surrounding the projection zones, or the arrival platform cortex, registers and interprets the material arrived at the first level. The third level, consisting of the great associative areas, which are the last to myelinate, correlates the data brought in by the various pathways. According to Orton, impairment of a level causes "cross over" of impulses from a lower level to the effectors, so that primitive patterns of reactions are produced. He called this return of primitive patterns "resurgence by defect." [22b] Orton stated the opinion that in catatonia there is an impairment of the third level of elaboration.[22a] In extremely deteriorated schizophrenic patients one may assume that the

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third, and partially the second, level of elaboration are impaired. In this way it is possible to explain both certain asymbolias and the short-circuiting processes which resurge by defect. It is now also possible to understand better the complex symptoms reported in the valuable contributions of Klüver and Bucy. The monkeys deprived of both temporal lobes also present visual asymbolia and primitive habits ("placing into mouth" or "oral tendency"). Since the great association areas have undoubtedly thalamic connections (Ariëns Kappers and associates [23]), it may be possible to find an anatomic interpretation of the emotional impairment.

All the foreging evidence suggests, but does not demonstrate, that the schizophrenic process either is organic in nature or at a certain stage is associated with organic changes. Goldstein's [24] position when he stated "I am inclined to assume that equivalent functional changes can be produced by organic, i. e., structural or clinical as well as by psychological derangement" may be maintained. He spoke also of "protective deterioration," after having described certain similarities between the impairment of abstract thinking associated with schizophrenia and that accompanying organic lesions.

The new phychosomatic concepts may also be resorted to. If Weiss and English's [25] formula, "psychologic disturbances → functional impairment → cellular disease → structural alteration," is accepted to explain the pathogenic mechanisms of cardiovascular and gastrointestinal conditions, why should it not be accepted to explain derangement of the nervous system, which is more directly under the fire of psychologic stimuli? The functions or structures which are phylogenetically more recent may be the ones more easily impaired, even by psychologic stimuli, so that when, after a long course, the impairment is complete or almost complete, resemblance may be obtained to lower levels of integration which have not yet acquired such functions or structures. Thus, the terms "regression" and "deterioration" would have the same meaning when applied to schizophrenic patients, unless by deterioration one wants to specify only the irreversibility of the syndrome; and for both may be substituted Lewis' [26] term "deviation."

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

VASOPRESSOR AND CAROTID SINUS SYNCOPE: CLINICAL, ELECTROENCEPHALOGRAPHIC AND ELECTROCARDIOGRAPHIC OBSERVATIONS. GEORGE L. ENGEL, JOHN ROMANO and T. R. MCLIN, Arch. Int. Med. **74**:100 (Aug.) 1944.

Engel, Romano and McLin report clinical, electroencephalographic and electrocardiographic observations on 18 persons subjected to syncope. Most of the subjects were examined on a tilt table. Before any special syncope-provoking procedure was attempted, the reaction to motionless standing for at least ten minutes was tested. The special procedures were initiated when it was clear that the postural response was normal. Reactions to syncope followed venipuncture, visceral distention, hyperventilation and stimulation of the carotid sinus, or they were associated with hypersensitivity of the carotid sinus reflex. The blood pressure was recorded as frequently as was practical, and continuous observations were made on the color of the skin, sweating, subjective responses and other changes.

Vasodepressor syncope was induced in 9 subjects by one of the aforementioned procedures. In addition, 6 subjects with the cardioinhibitory type of carotid sinus syncope and 3 subjects with the cerebral type were studied.

Unconsciousness, characterized by unawareness, muscular relaxation and falling, was always accompanied with high voltage slow waves in the electroencephalogram, regardless of the mechanism by which unconsciousness was provoked. Lightheadedness, giddiness and momentary loss of consciousness were associated with less obvious slowing of the electroencephalogram, loss of alpha activity or no change at all. In 2 subjects with the cerebral type of carotid sinus syncope the development of contralateral focal neurologic symptoms and signs without loss of consciousness was associated with abnormal waves from the ipsilateral cortex.

Vasodepressor syncope could be provoked by a wide variety of sensory stimuli, but the significance of the stimulus to the subject seemed to be more important than the specific modality involved. Most of the symptoms of vasodepressor syncope were associated with falling arterial blood pressure, and unconsciousness did not develop until the blood pressure had fallen to a low level. Symptoms were relieved by returning the subject to the recumbent position, but they often recurred if the subject stood up again, even if the original stimulus had been withdrawn. The derangement in circulatory dynamics was compensated for but not corrected by assumption of the recumbent position, presumably by avoiding the pooling effects of gravity. Recovery of consciousness may occur in the erect position; convulsive moments and increase in muscle tone seemed to aid recovery, but they were not essential. Muscular activity prior to assumption of an erect position prevents recurrence of syncope.

GUTTMAN, Philadelphia.

EXPERIMENTAL ANALYSIS OF THE FUNCTIONS OF THE BASAL GANGLIA IN MONKEYS AND CHIMPANZEES. MARGARET A. KENNARD, J. Neurophysiol. **7**:127 (March) 1944.

Kennard studied in monkeys and chimpanzees the effects of destruction by various routes of the different parts of the basal ganglia. She found that lesions of one or more of the nuclear complexes of the basal ganglia produced disorders of movement similar to the choreoathetosis and tremor seen in patients with involvement of these same regions. Choreiform movements appeared to any marked degree only in chimpanzees but developed in slight form in monkeys. The disturbances were always contralateral to the ablation, were transient and affected the arm and head more than the leg. Tremor, which was absent during complete rest but was present on movement or maintenance of posture, occurred in both chimpanzees and monkeys and was bilateral. Kennard concludes that two systems are present within the basal ganglia, yielding choreoathetosis and tremor respectively, and that these systems do not greatly influence each other nor can they be topographically distinguished. Kennard states that the relation of spasticity or rigidity to the basal ganglia has not been clarified but that isolated lesions of the basal ganglia in her animals did not alter resistance to passive manipulation. The addition of corticosubcortical lesions to pure cortical ablations augmented the increased resistance. Moreover, the removal of the basal ganglia after decortication increased the resistance which had followed decortication. The difference in results obtained in monkeys and in chimpanzees was associated with changes in the putamen and the extrapyramidal cerebral cortex and with the development of manual dexterity.

FORSTER, Philadelphia.

THE HIND BRAIN AND THE EARLY DEVELOPMENT OF BEHAVIOR IN FROGS. GING-HSI WANG and TSE-WEI LU, J. Neurophysiol. **7**:151 (May) 1944.

Wang and Lu studied the responses of tadpoles to tactile stimulation, both during their normal developmental states and after decapitation, transection of the neural axis at various levels and removal of one ear vesicle. Studies were also carried out on parabiotic twins, one of the pair being decapitated; and observations were made on normal, as well as on decapitated, tadpoles after immersion in solutions of potassium cyanide. Wang and Lu found that the duration of the tactile reflex decreased with increase in size of the tadpole. Decerebration or section of the dorsal portion of the cord had no effect on the duration of the reflex. Destruction of the rostral half of the hindbrain or transection of the surgical cord had no effect in embryos of 3 mm. length, but in larvae longer than 4 mm. the duration of the reflex was increased by these measures. During the early stages of cyanide poisoning the duration of the reflex was increased both in normal and in decerebrate preparations but was not affected in spinal and bulbospinal preparations. Spinal tadpoles were more active than normal or decerebrate larvae. Cyanide poisoning in its earlier stages increased the

spontaneous activity of normal and decerebrate tadpoles. Wang and Lu conclude that a mechanism is laid down in the cord of the tadpole for repeated reactions to brief tactile stimuli and that this mechanism is inhibited by impulses from the rostral half of the hindbrain. In an appendix, the authors point out that cyanide depresses the developing, as well as the adult, nervous system of the frog and that the last structure to mature is the first to succumb. Susceptibility to cyanide increases with the age of the embryo. FORSTER, Philadelphia.

EXPERIMENTAL HYPOGEUSIA FROM HORSLEY-CLARKE LESIONS OF THE THALAMUS IN MACACA MULATTA. H. D. PATTON, T. C. RUCH and A. E. WALKER, J. Neurophysiol. **7**:171 (May) 1944.

Patton, Ruch and Walker studied the capacity for gustatory discrimination for quinine hydrochloride in 10 immature Macaca mulatta monkeys before and after the production of bilateral electrolytic lesions of the posteroventral lateral nucleus of the thalamus. The lesions were produced under aseptic conditions and by means of the Horsley-Clarke apparatus. The authors found that the degree of damage to the posterolateral ventral nuclei as determined by microscopic examination could be correlated with the severity of the gustatory deficit. On the basis of these observations, the authors conclude that the evidence supports the hypothesis that taste fibers synapse in close association with fibers bearing somatosensory impulses from the face, mouth and tongue. Since the posterolateral ventral nucleus has no known connecting pathways with the uncus and hippocampal region and since this nucleus degenerates as a result of lesions of the sensory area for the face, Patton, Ruch and Walker conclude that their observations are in conformity with the hypothesis that taste is localized in the inferior portion of the rolandic area.

FORSTER, Philadelphia.

PHYSIOLOGICAL NEURONOGRAPHY OF SOME CORTICO-SUBCORTICAL CONNECTIONS IN THE CHIMPANZEE. H. W. GAROL and W. S. MCCULLOCH, J. Neurophysiol. **7**:199 (May) 1944.

Garol and McCulloch studied cortical connections in 7 chimpanzees under dial anesthesia, placing electrodes over the cortical surface and intracerebrally. By means of strychnine firing, the authors mapped the cortico-subcortical neuronal connections. They succeeded in demonstrating the following connections: (1) a cortico-caudate system from areas 8, 4s, 2 and 24; (2) a cortico-putamen system from areas 6, 4 and 1; (3) a corti-copallidal system to the external segment from area 6 and to the internal segment from what were questionably areas 4 and 5; (4) a corticopulvinar system from areas 40 and 39; (5) a corticothalamic connection from the arm subdivision of the central sector to the corresponding portion of the lateral thalamic nucleus.

FORSTER, Philadelphia.

THE ISOLATION OF THE ST. LOUIS ENCEPHALITIS VIRUS FROM CHICKEN MITES (DERMANYSSUS GALLINAE) IN NATURE. MARGARET G. SMITH, RUSSEL J. BLATTNER and FLORENCE M. HEYS, Science **100**:362 (Oct. 20) 1944.

Smith, Blattner and Heys report data which show that the St. Louis encephalitis virus is present in chicken mites (Dermanyssus gallinae) taken directly from chickens. These observations were made in the St. Louis area during a nonepidemic period. Other investigators have previously shown that the mosquito is a vector concerned in human epidemics of St. Louis encephalitis.

GUTTMAN, Philadelphia.

AFFERENT AREAS IN THE CEREBELLUM CONNECTED WITH THE LIMBS. E. D. ADRIAN, Brain **66**:289, 1944.

Adrian studied the electrical activity of the cerebellar cortex and the cerebellar subcortical afferent fibers in monkeys and cats. In a few instances electrical stimulation was used, but in most experiments mechanical stimulation of the skin, joints and muscles was employed.

Afferent discharges reaching the cerebellum by spinocerebellar and pontocerebellar pathways were recorded from a depth of 1.5 mm. below the cerebellar cortex. With this method it was possible to make a detailed map of connections. In both cat and monkey spinocerebellar discharges from the hindbrain arrive in the ipsilateral lobulus centralis, and those from the forelimb, in the culmen. Records of the afferent discharge in single units differ little from records of peripheral nerve fibers. A single afferent unit of the cerebellum may be connected with widely separated receptor organs. Pontocerebellar discharges to the lobulus centralis, the culmen and the lobulus simplex are derived from the hindlimb, the forelimb and the face region of the motor cortex. The receiving areas in these structures overlap those of the spinocerebellar pathway but extend farther laterally than the latter. The electrical activity of the cerebellar cortex consists of small potential waves of 150 to 250 per second, and afferent discharges result in increase of both frequency and amplitude. This effect tends to spread. In 2 dogs and 1 goat similar localizations were made. Adrian points out that the arrangement for afferent localizations is the opposite of that deduced for efferent localization by Connor and Graham.

FORSTER, Philadelphia.

POLIOMYELITIS IN BRITISH AND AMERICAN TROOPS IN THE MIDDLE EAST: THE ISOLATION OF VIRUS FROM HUMAN FAECES. J. R. PAUL, W. P. HAVENS and C. E. VAN ROOYEN, Brit. M. J. **1**:841 (June 24) 1944.

Attempts were made to isolate the virus of poliomyelitis from the stools in 35 cases of typical and atypical poliomyelitis which occurred during 1943 among British and American troops stationed in the Middle East. The following clinical types were studied: typical poliomyelitis, 15 cases; polioencephalitis with a short febrile course and paralysis limited to the cranial nerves, 5 cases; acute benign lymphocytic meningitis, 6 cases; localized neuritis following diarrhea or fever or both, 6 cases, and poliomyelitis contacts, 3 cases. Of the 15 cases of poliomyelitis, the stools were positive for virus in 9, in all of which the outcome was fatal. In all other cases the test for virus in the stools was negative.

ECHOLS, New Orleans.

Diseases of the Brain

ELECTROENCEPHALOGRAMS IN POST-TRAUMATIC EPILEPSY. HERBERT JASPER and WILDER PENFIELD, Am. J. Psychiat. **100**:365 (Nov.) 1943.

Jasper and Penfield studied electroencephalographically 81 cases of post-traumatic epilepsy. In 90 per cent a local area in one hemisphere was found in which random spikes or sharp waves were most prominent. In 69 per cent a relatively superficial focus was found in one area without significant abnormality elsewhere. Superficial lesions of the cortex were characterized by

random slow waves and random spikes or sharp waves. This type of activity was found in cases in which seizures occurred shortly after head injury. In 10 per cent of the cases generalized electroencephalographic disturbances were present, and in 3 cases diffuse multiple spikes and sharp waves appeared in the electroencephalogram and were virtually continuous. Bilaterally, synchronous abnormal discharges occurred in 6 cases. In 32 cases surgical extirpation of the seizure focus was carried out. In 94 per cent of this group the preoperative electroencephalogram was a reasonably accurate guide to the border zone of the lesion. In the cases of a single, discrete abnormality of the electroencephalogram surgical excision resulted in notable improvement in 71 per cent of cases, not only so far as incidence and severity of seizures were concerned but in the electroencephalographic pattern.

FORSTER, Philadelphia.

THE EEG IN LATE POST-TRAUMATIC CASES. MILTON GREENBLATT, Am. J. Psychiat. **100**:378 (Nov.) 1943.

Greenblatt studied by means of the electroencephalogram 263 patients who had had head injuries, followed by the appearance of symptoms varying from headache, with or without concomitant symptoms, to convulsions, fainting spells and personality changes. For 32 per cent Greenblatt found normal, for 20 per cent borderline and for 48 per cent abnormal records. Some correlation was present between the severity of symptoms and the degree of electroencephalographic changes; this was noticeable in the study of groups of patients but not in individual cases. No correlation between the interval after injury and the degree of the abnormality could be determined. Patients with post-traumatic seizures had a higher incidence of electroencephalographic abnormality; patients with headache, a lower frequency. It was impossible to correlate either the presence or duration of unconsciousness or the presence of skull fracture with electroencephalographic abnormalities. In the patients with post-traumatic psychoses the incidence of electroencephalographic abnormalities was greater than in the others. In the patients presenting focal electroencephalographic abnormality the focus coincided with the area of injury, skull fracture or deformity, or jacksonian seizures occurred, involving the contralateral extremities.

FORSTER, Philadelphia.

THE WATERHOUSE-FRIDERICHSEN SYNDROME. STUART W. COSGRIFF, Ann. Int. Med. **21**:187 (Aug.) 1944.

Cosgriff reports clinical and laboratory observations on 4 adults with the Waterhouse-Friderichsen syndrome. In the 2 patients for whom serum analyses were made a decrease in sodium and an increase in the nonprotein nitrogen were encountered. These observations are compatible with the results in cases of adrenal insufficiency but bear no relation to the extent of damage observed in the adrenal cortex at autopsy.

The role of hypoadrenalism in the mechanism of this syndrome is not yet established. Therapy should be directed chiefly against sepsis and secondarily toward the correction of possible associated adrenal cortex insufficiency.

GUTTMAN, Philadelphia.

MULTIPLE MENINGIOMA AND MENINGIOMAS ASSOCIATED WITH OTHER BRAIN TUMORS. SILVANO ARIETI, J. Neuropath. & Exper. Neurol. **3**:255 (July) 1944.

Arieti reports a case of multiple meningioma associated with an intracranial aneurysm and 2 other cases in which meningioma was associated with glioma. Microscopic studies and a review of the pertinent literature permit the author to conclude that the embryonal rests of Cohnheim and Ribbert giving rise to the tumors have an inherent neoplastic potentiality which manifests itself at different times in the glial and the meningeal tissues. In case 1 the tumors were all of meningeal origin, but were associated with an aneurysm. Arieti states that if "a developmental defect is considered as a necessary complementary factor in the pathogenesis of this vascular alteration, a local ontogenetic disorder may also be regarded as responsible for all the lesions found in that case."

GUTTMAN, Philadelphia.

A FATAL CASE OF CEREBRAL MALARIA. I. B. SNEDDON, Brit. M. J. **2**:814 (Dec. 25) 1943.

Sneddon reports the case of a man aged 28 who was admitted to the hospital in a semicomatose state, with a history of severe headache, vomiting and fever of three days' duration. There were no abnormal signs referable to the central nervous system. There was moderate leukocytosis; the complexion was muddy, and the pupils were contracted. Examination of the blood showed numerous ring forms of Plasmodium falciparum but no crescents. Twenty-four hours after the intravenous administration of 5 per cent dextrose in isotonic saline solution and the hypodermic injection of quinine dihydrochloride and epinephrine hydrochloride, the patient seemed greatly improved. However, despite continued treatment, he became worse and died on the fourth day after admission. Autopsy established the diagnosis of cerebral malaria. Sneddon presents this case "as a reminder that malaria should be considered in the differential diagnosis of coma and that unless treatment is started early, gross irreversible pathological changes occur in the brain."

ECHOLS, New Orleans.

GUNSHOT WOUNDS OF THE HEAD IN THE ACUTE STAGE. HUGH CAIRNS, Brit. M. J. **1**:33 (Jan. 8) 1944.

Cairns reports the results of a study of 459 men with nonpenetrating head injuries and 506 men with penetrating injuries to the brain. There were 3 deaths among the men with nonpenetrating injuries and 83 among those with penetrating injuries. Of the patients reaching the casualty clearing station in the North African campaign, 20 per cent died of cerebral damage within the next few days. After inadequate operative treatment, it was noted that about 1 of every 4 of the patients who were evacuated had complications of brain abscess or meningitis. However, it has been shown that when patients with head injuries can be segregated at the casualty clearing station, where radical operations are done within twenty-four hours of injury by trained neurosurgeons, the development of intracranial infections can be almost entirely eliminated. With regard to the bacteriology of head wounds, of 36 cases studied, bacteria were present in all but 1, with Staphylococcus aureus predominating. In most cases it was noted that the infection first developed superficially and then spread inward. Although there is still no definite evidence to support the view that sulfonamide compounds are active in the presence of pus, Cairns suggests further trial of these drugs in cases of head wounds in war zones. In a series of 23 men with cerebral wounds seen seventy-two hours after injury, local application of penicillin gave promising results, but further investigation of the technic of its application must be carried out.

ECHOLS, New Orleans.

AN UNUSUAL CASE OF CEREBRAL MALARIA. CHARLES S. D. DON and P. F. MEYER, Brit. M. J. **1**:149 (Jan. 29) 1944.

Don and Meyer report the case of a 22 year old soldier with cerebral malaria in whom 35 per cent of the red blood cells were infected with one or more parasites of Plasmodium falciparum. Thirty-six hours after administration of large doses of quinine dihydrochloride, the patient manifested pronounced cerebral symptoms and appeared to be dying, but responded to supportive measures, consisting of infusions and transfusions. Intensive quinine therapy for the next three days resulted in hyperpyrexia. Recovery was further complicated by hypostatic pneumonia.

ECHOLS, New Orleans.

HEAD INJURIES INVOLVING AIR SINUSES. D. MCKENZIE, Brit. M. J. **1**:652 (May 13) 1944.

McKenzie reports 10 cases of cerebrospinal fluid rhinorrhea due to fractures involving the air sinuses. In 4 cases the condition was the result of fracture by a penetrating missile, received in battle; in the remainder, to blunt injury. McKenzie concludes that indubitable signs that the dura has been torn and that meningitis may be imminent are the presence of cerebrospinal fluid rhinorrhea and intracranial aerocele. Anosmia is suggestive of local injury. Roentgenographic evidence of fracture may be easily overlooked. Preliminary treatment consists in prophylactic administration of sulfadiazine. One should make operative repair of the dura in every head injury with cerebrospinal fluid rhinorrhea rather than risk the dangers of natural repair. McKenzie used both unilateral and bilateral bone flaps. In each case the fistula was located by extradural exploration. There were no complications and no deaths in the author's series.

ECHOLS, New Orleans.

HEREDITARY FAMILIAL TELANGIECTASIS WITH EPISTAXIS AND MIGRAINE. A. M. G. CAMPBELL, Lancet **2**:502 (Oct. 14) 1944.

Campbell reports the case of a young man with telangiectasis whose mother and maternal aunt and grandmother also had the condition. He also had migraine, which preceded the attacks of bleeding from the nasal nevi. The bleeding, in turn, relieved the migrainous attacks. No focal signs pointed to involvement of the central nervous system. The condition had not seriously affected the longevity of the family.

MCCARTER, Boston.

ROLE OF PHYSICAL CONSTITUTION IN THE DEVELOPMENT OF DEMENTIA PARALYTICA. R. ORLANDO and M. ARNDT, Index neurol. y psiquiat. **4**:134 (Feb.) 1944.

Orlando and Arndt studied 214 patients with dementia paralytica from the point of view of Kretchmer's physical types. More than half the patients (52.3 per cent) were asthenic, as were most of the patients with depressive and agitated psychoses. There were more of the pyknic than of the asthenic type among patients with schizophrenic pictures. The asthenic habitus was more frequently associated with tabes in the simple and expansive forms. The number of patients is too small to justify the statement that any particular type is predisposed to the development of dementia paralytica.

SAVITSKY, New York.

Diseases of the Spinal Cord

SUBACUTE NECROTIC MYELOPATHY: A FATAL MYELOPATHY OF UNKNOWN ORIGIN. CHARLES DAVISON and SAMUEL BROCK, J. Neuropath. & Exper. Neurol. **3**:271 (July) 1944.

Davison and Brock report the cases of 3 young persons in whom a myelopathy, with a fairly rapid and fatal course, developed. The characteristic clinical features were progressive paraplegia; sensory impairment, with a level lesion; urinary disturbances, and abnormal findings in the cerebrospinal fluid, not typical of any specific lesion of the cord.

The anatomic features consisted of necrosis or softening of the spinal cord, most conspicuous in the lower dorsal and the lumbosacral region and involving both the gray and the white matter. In 1 case the pathologic process extended from the first cervical to the eighth thoracic segment. A syrinx of the cord and the lower part of the medulla was also present. There was no evidence of an inflammatory reaction. In the first case there was a pronounced mesodermal reaction; in the other 2 cases neither a glia nor a mesodermal reaction was evident.

The etiologic factors were undetermined in these cases, as well as in the other cases reported in the literature. Davison and Brock consider the disease in their cases to be subacute necrotic myelopathy, of unknown origin. They state that the term "myelitis" should be reserved for a condition of purely infectious origin.

GUTTMAN, Philadelphia.

RESULTS OF SURGICAL REMOVAL OF PROTRUDED LUMBAR INTERVERTEBRAL DISCS. BURTON M. SHINNERS and WALLACE B. HAMBY, J. Neurosurg. **1**:117 (March) 1944.

Shinners and Hamby made a follow-up study of patients operated on for herniation of the nucleus pulposus in the lumbar region. A total of 160 operations were performed on 140 patients (20 patients had 2 operations). Protruded disk was encountered in 116 patients, in 111 of whom the lesion was in the lumbar region. The 87 replies received from these 111 patients formed the basis for the figures compiled. Of this number, 49.5 per cent said they were cured, 48.3 per cent thought they were improved, and 2.3 per cent stated that in some ways they were worse than before operation. Fifty-four per cent had residual pain in the back, the leg or both; 87.4 per cent were working, only 4 having changed occupation; 20.3 per cent of the compensation group (28.4 per cent) still receive compensation; 57.3 per cent had pain in the leg or back on working; 92 per cent were glad they had the operation, and 4.8 per cent said they were sorry.

A striking parallelism in the results of operation was noted between patients receiving compensation and private patients.

WHITELEY, Philadelphia.

EPIDEMIC OF POLIOMYELITIS IN ZURICH IN 1937. W. ABEGG, Arch. f. Kinderh. **125**:166 (April 24) 1942.

Abegg reports observations on 167 patients with poliomyelitis in the course of the epidemic in Zurich, Switzerland, in 1937. The treatment consisted chiefly in the administration of serum and blood transfusions. The serum was a mixture of convalescent and so-called contact serum. The efficacy was not entirely convincing. Of the 167 patients, 62.3 per cent recovered; 19.2 per cent improved; 8.9 per cent did not improve, and 9.58 per cent died. Of the 16 patients who died, 7 were

moribund at the time of hospitalization. Follow-up observation revealed that in 10.8 per cent of the patients the paralysis was so severe that they will be severely handicapped for life. No defects aside from the paralysis remained. The severe meningitic symptoms produced neither impairment of intelligence nor signs of parkinsonism. The changes in character suggested by the parents of some of the children were the result of relaxation in discipline, due to pity rather than to organic changes.

J. A. M. A.

Peripheral and Cranial Nerves

CRANIAL-NERVE PALSIES WITH HERPES FOLLOWING GENERAL ANAESTHESIA. J. H. HUMPHREY and MARGARET MCCLELLAND, Brit. M. J. **1**:315 (March 4) 1944.

Humphrey and McClelland report 13 cases of cranial nerve palsy following anesthesia, in 2 of which the outcome was fatal. The use of no one anesthetic was common to all cases. The severity of the condition varied from subjective trigeminal anesthesia to encephalitis. Twenty-four to forty-eight hours after administration of a general anesthetic the patients complained of a sense of coldness, numbness or tightness around the lips, which spread along the whole distribution of the fifth nerve on both sides. Difficulty in swallowing was also experienced. Circumoral herpes of the febrile type appeared on about the third postoperative day. The fifth and seventh nerves were most frequently involved, but the third, fourth, sixth, tenth and twelfth cranial nerves were affected in some cases. When improvement occurred, it began from the fifth to the tenth day; rapid recovery followed in cases of milder disturbance, whereas with the more severe form residual subjective changes were still apparent five months later. Clinical evidence and the results of experimental investigation strongly favor a toxic theory. The authors suspect that trichloroethylene, which had been used in the anesthetic machine, had combined with the soda lime, with the production of dichloroacetylene, and they conclude that, until further investigations have been made, trichloroethylene should not be used where there is any possibility of its coming in contact with soda lime.

ECHOLS, New Orleans.

EARLY DIAGNOSIS OF PERIPHERAL NERVE INJURIES IN BATTLE CASUALTIES. W. R. RUSSELL and A. B. HARRINGTON, Brit. M. J. **2**:4 (July 1) 1944.

Russell and Harrington describe in detail neurologic methods for examination of wounded extremities for nerve injury. These procedures can be used by surgeons in forward battle areas. Illustrations of the methods are included. A simple technic of recording nerve function is explained. The dangers of excessive splinting of the fingers in the early treatment of nerve injuries are emphasized. Maintenance of range of movement of the joints is all that is necessary in the early treatment of injuries to the nerves of the lower extremity. The importance of attention to the patient's morale is stressed.

ECHOLS, New Orleans.

SUPERIOR SULCUS TUMOR (PANCOAST). B. A. DORMER, F. J. WILES and J. FRIEDLANDER, Lancet **2**:312 (Sept. 2) 1944.

Dormer, Wiles and Friedlander describe a case of a tumor of the superior pulmonary sulcus associated with pain in the shoulder and arm, Horner's syndrome and signs of pressure on the ulnar nerve. There was roentgenographic evidence of infiltration of the apex of the lung, but not of involvement of bone. As a result of complete paralysis of the right recurrent laryngeal nerve, there was inability to shout or sing. The condition was inoperable. A specimen was taken for biopsy, but it was impossible to be certain of the origin of the tumor. The general structure was not unlike that sometimes seen in carcinoma of the bronchus.

Pancoast stated the belief that the type of tumor to which his name has been attached comes from a remnant of the branchial cleft. His syndrome may be due to this or to any other tumor of the superior pulmonary sulcus. All authors are agreed that, in view of their location, such neoplasms are always fatal.

MCCARTER, Boston.

NEUROLOGICAL COMPLICATIONS OF SERUM AND VACCINE THERAPY. R. R. HUGHES, Lancet **2**:464 (Oct. 7) 1944.

Hughes reports 6 cases of neurologic complications following serum or vaccine therapy. Other authors have pointed out that of all serums, vaccines and antitoxins, tetanus antitoxin most commonly causes complications of this nature. Allen classified such complications into four types: radicular, neuritic, polyneuritic and central. In the radicular type which occurs in half the cases, an attack of serum sickness occurs five to ten days after injection of serum, and pain, weakness and wasting develop in the shoulders. Sensory changes are slight or absent. The neuritic type is confined to a peripheral nerve, with onset of paralysis twenty-four to forty-eight hours after the appearance of serum sickness. The polyneuritic type is characterized by generalized peripheral neuritis. The central type shows "evidence of cerebral involvement, usually papilledema accompanied in some cases by a meningeal reaction or focal cerebral lesion." The cranial nerves have also been reported to be involved.

Hughes points out how closely these complications resemble the disturbances said to be due to virus infection. "Further investigation of the etiology of these conditions is urgently required."

MCCARTER, Boston.

Treatment, Neurosurgery

BORDERLINE CASES TREATED BY ELECTRIC SHOCK. ABRAHAM MYERSON, Am. J. Psychiat. **100**:355 (Nov.) 1943.

Myerson reports the results of electric shock therapy in 10 cases in which either the patient was noncommittable or the condition was not amenable to clearcut diagnosis. These cases included instances of fixed depressive ideas, depressive states relating to real life situations, obsessive-compulsive states, anhedonic unreality and, in 1 case, anorexia nervosa, which shifted to bulimia. Treatments were administered in the outpatient department, with temporary improvement in each case.

FORSTER, Philadelphia.

RESULTS OF HOSPITAL TREATMENT OF ALCOHOLISM. JAMES H. WALL and EDWARD B. ALLEN, Am. J. Psychiat. **100**:474 (March) 1944.

Wall and Allen report the results of hospital treatment of 100 men admitted because of alcoholism. Eighty-one of the series had no psychosis. There was a high incidence of alcoholism among the relatives of

the patients. In 59 cases the mothers of the patients had been oversolicitous and the fathers had been successful and forceful. Study of the sexual life and the social and interpersonal relationships of the patients revealed precarious adjustments. Drinking had usually begun at an early age and had been continued for long periods, the average being fifteen years. The authors recommend a period of treatment of six months to a year. The therapeutic regimen consists in attention to physical defects, physical therapy and psychotherapy, the last being directed toward appreciation of the gravity of the situation and the underlying psychologic features, the need for total abstinence and the evaluation of the patient's assets. Follow-up studies revealed that 33 per cent did not improve, 19 per cent were drinking, but their condition had improved and 24 per cent were recovered.

FORSTER, Philadelphia.

PERIPHERAL NERVE SURGERY: TECHNICAL CONSIDERATIONS. R. GLEN SPURLING, J. Neurosurg. **1**:133 (March) 1944.

In this article the technic and routine followed in treatment of peripheral nerve injuries at the Walter Reed General Hospital are described. Among the general principles advocated is the postponement in closure of battle wounds until they are reasonably clean. Two weeks after this secondary suture exploration for nerve repair is performed. At this time chemotherapy, hemostasis, mobilization and correct positioning of joints, freedom from nerve tension and nerve transplantation are important items of treatment. At operation electrical stimulation of exposed nerve trunks is valuable in diagnosis of anatomic severance.

This hospital follows the radical exposure of peripheral nerve injuries in all cases except those in which the symptoms show rapid improvement. If impulses still traverse the scar, only neurolysis is effected; end to end suture is performed in cases of complete severance. Use of fine tantalum sutures and cuffs of tantalum foil has facilitated successful nerve anastomosis.

WHITELEY, Philadelphia.

TREATMENT OF THE PAINFUL PHANTOM LIMB BY REMOVAL OF POST-CENTRAL CORTEX. C. G. DE GUTIÉRREZ-MAHONEY, J. Neurosurg. **1**:156 (March) 1944.

De Gutiérrez-Mahoney believes that pain is felt in every case of phantom limb; which, in turn, nearly always follows amputation, but that it is seldom disabling. The exact cause of the condition has not yet been determined, but it is probably due to stimulation of peripheral nerves, with the pulses reaching consciousness.

The simplest and most effective way of dissolving this phantom is to interrupt the centripetal pathway by removing the corresponding portion of the postcentral cerebral cortex. The author reports a case in which operation was performed more than two years before, with no recurrence of symptoms.

WHITELEY, Philadelphia.

TREATMENT OF MENINGOCOCCAL MENINGITIS WITH PENICILLIN. MANSON MEADS, H. WILLIAM HARRIS, BERNADO A. SAMPER and MAXWELL FINLAND, New England J. Med. **231**:509 (Oct. 12) 1944.

Meads, Harris, Samper and Finland report observations on 9 unselected patients with meningococcic meningitis admitted to the Boston City Hospital during April 1944. The ages of the patients ranged from 14 to 58 years. Seven patients were acutely ill and irrational. One was acutely ill and rational, and 1 was only moderately ill when first seen. The duration of the acute illness before hospitalization varied from one to seven days, with an average of about three days. The usual laboratory studies, including examination of the cerebrospinal fluid, were performed. Five of the patients had concomitant meningococcemia. All the patients were given the calcium salt of penicillin intrathecally and intramuscularly.

The clinical response to penicillin is slower than that to the sulfonamide compounds, for the following reasons: Biochemical and bacteriologic abnormalities in the spinal fluid persist longer; there may be recurrences; the meningococcus carrier state may persist; the treatment is difficult, and, finally, one may eventually have to resort to the sulfonamide compounds. Also, strains of the type I meningococcus vary greatly in their susceptibility to penicillin. Those studied in this series of patients resembled the relatively resistant strains of Staphylococcus aureus and Streptococcus viridans.

The authors conclude from their observations that the sulfonamide compounds are the drugs of choice in the treatment of meningitis due to the type I meningococcus and that penicillin may be effective in treatment of this form of meningitis in the doses used (from 190,000 to 1,155,000 Oxford units). However, the response is less favorable than that following the use of sulfonamide compounds.

GUTTMAN, Philadelphia.

THE TREATMENT OF SCIATICA: AN ESSAY IN DEBUNKING. ARTHUR HURST, Brit. M. J. **2**:773 (Dec. 18) 1943.

Numerous and divergent views regarding the pathogenesis of sciatica have been expressed, and the methods of treatment have been as varied. A review of the therapy of sciatica from 1901 to 1943 corroborates this statement. Methods which have been tried include injection of various drugs into the nerve, the intervertebral space and the myalgic spots; manipulation; application of plaster cast; removal of herniated intervertebral disk or lateral intervertebral joint, and the application of "fuming hydrochloric acid." As a rational method of treating sciatica, Hurst recommends complete rest in bed from the onset of symptoms, with immobilization in a plaster spica only in cases of severe pain. With this procedure, he insists on simple psychotherapy, which promotes the expectation of rapid and complete recovery. A few patients, who fail to respond after one month of such conservative treatment, will probably require relief of root pressure by removal of a herniated intervertebral disk.

ECHOLS, New Orleans.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

Regular Meeting, April 28, 1944

Spontaneous Subarachnoid Hemorrhage with Coarctation of the Aorta: Report of a Case with Recovery. DR. RICHARD HEARNE.

Coarctation of the aorta is a rare condition. This fact, together with the neurologic changes in the present case, suggests that a report would be of interest.

REPORT OF CASE

H. A., a Negro aged 21, unmarried, entered the Philadelphia General Hospital on Jan. 3, 1944. He had been rejected for Army service in the fall of 1943 because of "heart trouble," but his mother declared that he had always been healthy until the day before admission to the hospital. At that time he suddenly had a severe bursting headache, followed by fever, sweats and cramps in his neck, back and legs.

Examination on admission was incomplete because the patient was irrational, hyperactive and uncooperative. The neck was rigid; the deep reflexes were hyperactive throughout; the Brudzinski and Kernig signs were present, and the patient was incontinent of urine and feces. The spinal fluid contained bright red blood, the last of the specimen being as bloody as the first. The blood pressure in the right arm was 220 systolic and 125 diastolic. Except for leukocytosis, with a count of 18,200, the results of laboratory studies were without significance.

Three days after admission to the hospital the patient was transferred to the neurologic service of Dr. A. S. Tornay. Examination revealed that the patient was strong and well developed. He was lying in a position of opisthotonos, was stuporous and did not respond to efforts made to arouse him. The neck was rigid, and the head was turned sharply to the left and fixed in that position. The deep reflexes were somewhat increased in the right arm and leg, and there was increased resistance to passive motion in these limbs. The abdominal and cremasteric reflexes were absent. The spinal fluid was still uniformly bloody.

Examination of the chest showed enlargement of the heart, and there was a diffuse, heaving apical impulse. A high-pitched systolic murmur could be heard over the entire precordium. However, the most characteristic feature of this murmur was a pronounced, bilateral parasternal accentuation, which even extended down into the epigastrium. A diastolic murmur was also heard over the aortic area and in the left third interspace. Deep subcutaneous vessels, approximating in size that of a normal radial artery, could be felt pulsating over the chest. These vessels were especially numerous in the infrascapular and subscapular regions. The pulse over the femoral arteries was small and weak, with a definite lag when it was compared with the radial pulse. Neither the pulse in the popliteal artery nor that in the dorsalis pedis artery could be felt on either side. The blood pressure was 205 systolic and 80 diastolic in the right arm and 150 systolic and 75 diastolic in the left arm. No blood pressure could be obtained in the legs.

Roentgenograms of the chest showed a moderately enlarged heart with a configuration characteristic of hypertension. There were prominence of the ascending aorta and absence of the aortic knob of the descending aorta. However, the lower margins of the ribs were only slightly eroded. An electrocardiogram showed beginning left axis deviation.

The patient's neurologic signs and his headache gradually subsided after a stormy course of a few days, during which he was kept under heavy sedation. He was discharged home, apparently completely recovered, three and a half weeks after admission.

Comment.—This patient presented a classic picture of coarctation of the aorta with one of its commoner complications. The principal points in establishing the clinical diagnosis were: (1) hypertension in the arms, (2) absence of detectable pulse or blood pressure in the legs, and (3) demonstration of the collateral circulation circumventing the obstructed aorta.

DISCUSSION

DR. ANTHONY S. TORNAY: This patient was admitted to the Philadelphia General Hospital with the classic signs and symptoms of meningeal irritation. He was sent to the fever ward, and his condition, at the time of admission, was suspected to be meningococcic meningitis. A spinal tap revealed bloody spinal fluid. Several days later the patient was reassigned to service 2 of the neurologic ward.

At this time I felt the patient's condition was malignant hypertension, with one of its complications, spontaneous subarachnoid hemorrhage. The course was very stormy; and when he began to improve, I was surprised to have the resident, Dr. Hearne, ask me whether I could detect any pulsations of blood vessels of the lower extremities on palpation. I failed to feel the pulsations of the tibial or the popliteal vessel. Also, it was impossible to obtain blood pressure readings in either lower extremity. On close examination there was also noted some dilatation of the superficial blood vessels over the chest. This, with the roentgenographic confirmation of the clinical diagnosis of coarctation of the aorta, led my colleagues and me to believe we had an unusual problem in this patient.

The following points should be emphasized in connection with this condition. First, in about 13 per cent of all cases of coarctation of the aorta a vascular complication exists. A vascular anomaly in one part of the body sometimes means that other vascular abnormalities are present. Furthermore, the elevation of the blood pressure above the thorax leads to intracerebral complications.

The patient improved, walked out of the hospital and is walking about the streets of Philadelphia, with the "sword of Damocles" hanging over his head.

DR. HELENA RIGGS: My associates and I have studied the incidence of miliary aneurysm in about 2,000 consecutive autopsies and, oddly, we have found no coincidence with congenital defects of the heart. In all the 45 cases in which ruptured aneurysm was present there was an associated chronic degenerative cardiovascular disease, but not of the congenital type.

DR. GEORGE D. GAMMON: Dr. Hearne has done a service in calling attention to another cause of spontaneous subarachnoid hemorrhage. Few of the textbook discussions of the cause of this condition include coarctation of the aorta. I believe Brain mentioned it in his book. I looked up the matter at one time, when I was studying the case of a patient at Children's Hospital, in the service of Dr. James Reilly.

A boy aged 11 years had a sudden onset of headache followed by stupor and was admitted to the hospital with a diagnosis of meningitis. The blood pressure in both arms was 160 systolic and 110 diastolic. The neck was stiff, and he was semistuporous. Spinal puncture revealed fresh blood, without xanthochromia.

Over the heart was noted a loud, blowing systolic murmur, best heard to the left of the sternum in the third inner space. After spinal puncture the boy showed improvement for five days, during which time renal studies were carried out in order to determine the mechanism of the hypertension.

Urinalysis gave entirely normal results except for specific gravity of 1.016 and, on one occasion, 1.007, with fluctuation between these levels. A urogram of the kidney revealed nothing abnormal except for slight ptosis. These negative results led to reexamination of the patient in an effort to determine the cause of the hypertension.

The resident, Dr. E. P. Morris, noted that the blood pressure was unobtainable in the lower extremities. The intercostal arteries were pulsating, and two large arteries passed downward on the lateral thoracic wall from the axilla for a distance of about 6 inches (15 cm.).

Roentgenographic study showed no evidence of erosion of the ribs. The heart was slightly enlarged on the right side but otherwise appeared normal in the roentgenogram. A clinical diagnosis of coarctation of the aorta was made.

The boy continued to improve for a week and then suddenly became stuporous and cyanotic, and the blood pressure rose to 250 systolic and 170 diastolic. He was bled from the brachial artery; but the blood pressure fell only to 190 systolic and 170 diastolic, and he died of respiratory failure.

Lumbar puncture revealed fresh blood, and it was believed that he had had another hemorrhage.

Autopsy was confined to the chest. The right side of the heart was enlarged. The left ventricle showed extreme hypertrophy. At the site of the ductus arteriosus the aorta narrowed abruptly to about 0.8 cm. in external diameter. Beyond this point it ballooned out to form an unusually prominent thoracic segment, which narrowed down to normal size only at about the level of the diaphragm.

The intercostal arteries were all prominent, particularly the first and second. At the constriction, the aorta permitted the passage of a 2 mm. probe. The lumen of the ductus arteriosus was obliterated.

The kidneys showed little change, but an occasional glomerulus had undergone thickening of the capsule and partial hyalinization. In other words, the condition was not renal hypertension. The larger blood vessels of the kidney were not abnormal.

Unfortunately, I could not examine the brain, and I do not know the condition of the vessels there; but from the clinical picture there seems little doubt that the boy died of subarachnoid hemorrhage. He had a history of minor headaches, but nothing of any significance before this sudden onset of hemorrhage.

I should like to ask Dr. Hearne how many cases of spontaneous subarachnoid hemorrhage with coarctation of the aorta have been reported in the literature. In what percentage of cases is subarachnoid hemorrhage due to coarctation of the aorta?

DR. RICHARD HEARNE: In 1928 Hamilton and Abbott reported a total of 211 cases of coarctation of the aorta verified at autopsy (*Am. Heart J.* **3**:381, 1928), and in 20 of this number death was due to cerebral hemorrhage. In 18 of these cases the hemorrhage was subarachnoid. Since 1928, 2 cases of subarachnoid hemorrhage have been reported in the literature. The number of cases similar to the one reported here is probably small.

Meningitis Due to Infection with Torula Histolytica: Report of a Case. DR. JOSEPH E. SNYDER.

The first report of a case which can be almost surely identified as one of torulosis of the central nervous system was made by Zenker in 1861. At the present time less than 100 cases have been recorded. The organism responsible for this unique disease was carefully studied by Stoddard and Cutler in 1916. They named it Torula histolytica, which Freeman and Wiedman considered a misnomer because their studies indicated that it does not have lytic properties for nerve tissue.

T. histolytica is a pseudoyeast which involves many internal organs, particularly the brain and the spinal cord, presenting three types of lesions. These lesions may be, first, diffuse granulomatous meningitis; second, small granulomas or cysts in the cortex, and, third, deeply placed lesions, sometimes solid but more often cystic. The disease apparently does not occur frequently enough, or is not diagnosed often enough for it to be considered in the differential diagnosis as often as it should be. Torular infection should be considered in cases of atypical meningeal irritation in which the usual pyogens are not encountered. India ink preparations of the spinal fluid provide a ready means of identification of the organism and differentiate between the torulas and red blood cells, for which the organisms are often mistaken.

The following case is reported because it is, to my knowledge, the first case in which penicillin was employed and because its pathologic lesions, particularly those of the central nervous system, were studied.

E. M., an 8 year old white girl, was well until two and a half years before her admission to the University Hospital, when there developed an acute staphylococcic osteomyelitis of the femur and humerus which was refractory to sulfathiazole and became chronic, with sequestration and the formation of multiple draining sinuses. On admission to the hospital for penicillin therapy of the osteomyelitis, she had multiple draining sinuses, mild weakness of the right sixth nerve and definite nuchal rigidity and complained of frontal headache, which she had noted for the preceding two weeks. The vital signs were normal except for a slight elevation of blood pressure. The blood and urine showed no abnormalities. Twenty-four hours later she suddenly became comatose, at which time the head and eyes turned to the left with lateral nystagmus, and she went into opisthotonos with generalized rigidity except for paralysis of the right side of the face. Thirty minutes later she regained consciousness and seemed fairly alert. Three lumbar punctures at five day intervals showed the spinal fluid to be under increased pressure. The fluid obtained on the first tap was slightly blood tinged, but the succeeding two specimens were clear. Microscopic examination revealed between 60 and 100 cells per cubic millimeter in each of the specimens of fluid, which were reported as red blood cells but were probably torulas. Cultures of the first two specimens showed an organism which was reported as "Monilia" and was regarded as a contaminant. The third specimen re-

vealed the same organism, which, when examined in india ink preparations, was shown to be T. histolytica. The penicillin, which had already been given in the amounts of 90,000 Oxford units daily, was increased to 120,000 units, supplemented by intrathecal administration of 10,000 units daily. In addition, large doses of sodium iodide and sodium sulfadiazine were given intravenously. The patient appeared to improve for a short time; then, although she had received a total of nearly 3,000,000 units of penicillin, she began to have numerous convulsive seizures and died of sudden spontaneous bilateral pneumothorax.

At autopsy, the most striking lesions were found in the brain. The meninges were smooth and glistening, but the subarachnoid and ventricular fluid was pearly gray and cloudy. The brain was fixed in solution of formaldehyde U. S. P., in 1:10 dilution, for one week. Transverse sections of the brain revealed many small single multilocular cysts, occurring chiefly in the gray matter of the frontal and parietal lobes. These cysts were sparsely scattered over the ependymal surfaces of the cerebellum. The entire basal ganglion system was replaced by a mass of multilocular cysts containing a pearly gray, gelatinous material. Microscopic examination revealed the cysts to be extremely thin walled, with no surrounding inflammatory reaction. The adjoining cells appeared to be somewhat compressed. The cysts contained large numbers of the torulas. The torulas were also seen in the meninges, but there was no inflammatory reaction. The lungs showed small blebs over the pleural surfaces, extending down into the parenchyma. The liver, spleen and lymph nodes were greatly enlarged. Histologic studies showed small cyst formations containing torulas in all organs except the heart muscle, including the vertebral marrow and the retina. The normal architecture of the lymph nodes was completely destroyed and replaced by variously sized, thin-walled cysts containing torulas. It is of interest to note that numerous antemortem and a postmortem blood culture failed to show the organism.

In this case the portal of entry of the organism could not be determined. The diagnosis was delayed by failure to recognize the torulas in the spinal fluid, the organisms being mistaken for red blood cells. Previous case reports indicate that in many instances these organisms have been similarly mistaken for red blood cells or for lymphocytes. Penicillin in the dosage employed failed to alter the course of the disease, though the osteomyelitic process promptly subsided.

DISCUSSION

DR. HELENA RIGGS: Dr. Snyder is to be congratulated that the diagnosis was made before death. I have had 2 cases of blastomycotic involvement of the central nervous system, in both of which the diagnosis was made post mortem. The clinical aspects of these cases were so dissimilar that it might be well to outline the symptoms.

The first case was that of a physician aged 50 who, during a period of a year and a half, showed pronounced mental deterioration. He was brought into the Philadelphia General Hospital with a presumed diagnosis of dementia paralytica, which was not confirmed serologically. While in the hospital, he showed such emaciation that a diagnosis of amyotrophic lateral sclerosis was considered. He died with the diagnosis unestablished. There had been no signs referable to meningeal irritation.

At autopsy the meninges showed extreme thickening and a "boiled egg white" appearance, and the brain was shrunken.

Histologic examination revealed chronic meningitis of both the brain and the spinal cord, with torulas around the choroid plexus and over the base of the brain. The diagnosis was confirmed by Dr. F. Weidman.

The second case was that of a Negro youth aged 17. He was admitted to the hospital with a history of severe headache, stiff neck and coma and died six hours after admission, eighteen hours after onset of the first symptoms. The spinal fluid contained 800 polymorphonuclear leukocytes per cubic millimeter, with a sterile culture. The condition in this case was not torulosis, but sporotrichosis.

At autopsy there were bruiselike areas over one surface of the brain, and histologic examination showed a myriad of yeastlike, or fungus-like, organisms filling these areas and the subarachnoid space, with a secondary reaction of lymphocytes.

In the first case the condition of the nervous system was extremely chronic, without signs of meningeal irritation; in the second case there was a picture of acute purulent meningitis.

DR. MATTHEW MOORE: The case reported by Dr. Snyder is truly an extraordinary one in view of the wide dissemination of the so-called torulas, involving practically every organ of the body. At this point, may I indicate that the organism is not a torula; neither is it histolytic, but, as Dr. Snyder intimated, properly belongs to the cryptococci—Cryptococcus hominis, or Cryptococcus meningitidis.

It is important to emphasize what Dr. Riggs has stated with regard to the symptoms in cases of torulosis. A review of the reported cases indicates that almost invariably, with the exception of a few cases in which the diagnosis was made ante mortem, the clinical diagnoses have been chiefly brain abscess, brain tumor or tuberculous meningitis. Tuberculous meningitis seems to have been the most frequent diagnosis, because of the rather chronic course of the disease.

Dr. Greenfield and I presented before this society a case of cryptococcic meningoencephalitis in which the meninges and brain were notably involved (Meningoencephalitis Due to Cryptococcus Hominis, ARCH. NEUROL. & PSYCHIAT. **40**:1054 [Nov.] 1938). More recently, we have examined the brain of a man aged 68 who had been in the Graduate Hospital of the University of Pennsylvania during the early part of 1943. He had complained of intense headache for about eight days before his admission. The clinical diagnosis was either abscess of the brain or glioma. Ventriculographic studies were carried out, and subsequently operation was performed for a tumor of the temporal lobe. No tumor was exposed. He died eight days after operation. Tissue studies of the brain revealed intense meningoencephalitis, due to cryptococcic meningitis. It may be pointed out that in cryptococcic invasion the meninges are not involved alone, but there is an accompanying involvement of the brain itself. There is no inflammatory reaction on the part of the brain tissue. It merely is pushed aside and compressed by the growth of the cryptococci and does not undergo histolytic change, nor is there inflammation or glial reaction of any note at the periphery of the cerebral lesions.

Did Dr. Snyder note foreign body giant cells in his case? In some cases huge, multinucleated giant cells have appeared in or about the cerebral lesions, a feature reported in our first case.

I wish that Dr. Snyder would express an opinion regarding the possible relation of the widely scattered

lesions to the use of penicillin, in that this drug, instead of aborting the disease, may have acted symbiotically and thereby have contributed to the dissemination of the lesions throughout the body.

DR. JOSEPH E. SNYDER: In the examination I saw a cell that could be considered a giant cell. Such cells were certainly rare.

With regard to the effect of penicillin I am uncertain. If penicillin did no more, it retarded the progress of the "osteomyelitis," and if the organism entered the body through the draining sinuses and was present in these sinuses, their healing should have some effect on the organism, but certainly not a curative one.

DR. D. SCOTT: In view of the careful way in which the clinical material has been assembled in this case, it is interesting to restudy the electroencephalogram, with particular attention to the pertinent information which it brought to light.

At the time this patient was studied, he had been recently admitted to the hospital, and the diagnosis was uncertain. However, some examiners expressed the opinion that possibly the disorder was focal epilepsy.

From the electroencephalogram which shows simultaneous tracings from the left and the right temporal area, one can see that there is complete symmetry of the pattern, which is characterized by the appearance of persistent, slow, irregular waves. This type of activity was obtained from all areas of the cortex, although it was slightly more prominent in the left frontal area than elsewhere. This was reported as indicating the existence of a diffuse, degenerative process, and it was stressed that there was no evidence in favor of a single irritative focus. It is now known that such a diffuse process was present, which was both degenerative and pressure producing, thus giving optimum conditions for the type of cortical irritation that usually results in prominent electrical activity.

While the electroencephalogram, of course, is only one of several means which helped in arrival at the diagnosis, I believe it was a valuable contribution in this instance because of the possibility of obtaining a clearcut differentiation between a focal and a diffuse lesion.

DR. GEORGE D. GAMMON: Can Dr. Snyder state where these organisms live outside the human body?

DR. JOSEPH E. SNYDER: So far as I am aware, no one knows where these organisms live. There are other species that are fairly omnipresent, but this particular organism has not been seen except in cases of cryptococcic meningitis.

Reeducation of the Aphasic Patient. DR. FRANK P. BAKES.

The speech examination of an aphasic patient is primarily a matter of psychologic testing, with a view to determining what intellectual functions are intact. My colleagues and I try to determine what sensory avenues are available for training and what motor abilities remain for expression. We test particularly for auditory and visual function, on the sensory side, and for ability to write and speak, on the motor side. We also determine whether he can understand what he writes and whether he can write from dictation, either in print or in script.

Most aphasic patients are under considerable emotional tension and are beset with worries. Our approach then leads us to sympathetic handling and understanding. We must also provide reassurance and encouragement because these persons are easily discouraged, as a result of their slow progress.

I should like to describe briefly two methods which have not yet been employed extensively but which seem to give promise of effective use. The first is known as the motokinesthetic method, originated by Sara M. Stinchfield and Edna Hill Young (Children with Delayed or Defective Speech, Stanford University, Calif., Stanford University Press, 1938). This method was devised especially for the speech training of children with delayed speech, but it has been found useful for other types of speech disorders. The method consists primarily of actually manipulating the articulatory organs in such a way as to help the subject gain a kinesthetic impression of the proper position of the lips, tongue, jaw, etc., in producing the various speech sounds. For example, to quote from Stinchfield and Young, "to produce the 'p' sound, let the trainer place his thumb and forefinger below the lower lip, moving it upward until the two lips meet in closed position, not allowing them to become taut in that position or to press upon each other with any degree of tension. Immediately upon the closure, the trainer, without lifting her hand from contact with the jaw, brings the lower lip and jaw downward, usually securing the 'puff' in question as the lower lip parts from the other."

Another method, reported by Grace Fernald (Remedial Techniques in Basic School Subjects, New York, McGraw-Hill Book Company, Inc., 1943), is known as the kinesthetic method and is used primarily as a remedial technic in teaching the basic school subjects. The method could well be called a "tactual kinesthetic" technic, as a great deal of emphasis is placed on the importance of finger contact with the paper on which a word is written or printed. In this procedure, the teacher writes in large script in crayon on a strip of paper the word which the child is to learn. The child then traces the word with his index finger, sounding it as he progresses through the word. After a few repetitions, he writes the word without copying it. This is especially effective in cases of disturbances in spelling and reading. Dr. Fernald suggests that she and her associates ignore the matter of handedness and seem to secure good results without emphasis on training the dominant hand.

DISCUSSION

DR. HENRY WYCIS: Has Dr. Bakes tried the use of music in the reeducation of aphasic patients? This might be of special interest in view of the fact that some aphasics can sing words and tunes whereas they are unable to speak them.

DR. MATTHEW MOORE: What hope of success can Dr. Bakes offer a patient who has had aphasia for two or three years?

DR. FRANK P. BAKES: I cannot say, for we have not used the method long enough to determine that. In the cases I reported, I think that the training was begun shortly after onset of the aphasic condition.

We hope to employ these methods with some of the patients we are getting. We did start with 1 patient last summer; unfortunately, after only a few weeks, he was unable to continue, and we were unable to evaluate the results.

CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *President, in the Chair*

Regular Meeting, May 9, 1944

A Complication of Prefrontal Lobotomy. DR. LLOYD H. ZIEGLER† and DR. CARROLL W. OSGOOD, Wauwatosa, Wis.

The cases of 7 of 16 surviving patients were reported in which edema or bullae (or both) of the lower extremities appeared soon after prefrontal lobotomy. Theoretic possibilities, such as injury to the cortical center for the leg and foot and the paracentral lobule and the branches of the anterior cerebral artery were discussed.

The authors stated that basic research is needed to explain this complication, which is usually mild and passes away in a month or two. They expressed the opinion that a larger opening in the skull should be made to deal better with anomalies of the brain and skull that might be encountered.

DISCUSSION

DR. PERCIVAL BAILEY: The first roentgenogram seemed to indicate that the incision was too far back. It seemed to be 1.5 cm. back of the coronal suture. It must have entered the hypothalamus. That may explain in part the symptoms referable to the rectum and bladder. The illustration does not represent the usual course of the anterior cerebral artery. The artery usually has a large branch which leaves the corpus callosum for the callosomarginal sulcus, leaving only a small minor branch passing over the corpus callosum.

DR. CARROLL W. OSGOOD, Wauwatosa, Wis.: We were interested in the fact that no one else had reported this complication, and we wondered why that was. It may be that surgeons did not have the patients under as close observation as we had in the sanatorium. We thought it worth while to call attention to this edema, as other reports may be made to bear out our observation. Two patients had considerable edema of the legs prior to operation and did not have it afterward. One was a very agitated woman, who stood practically all the time. The edema in her case may have been hypostatic. Since the operation, she is more active, and the edema has disappeared.

DR. PAUL C. BUCY: It is probably erroneous to say that this edema has to do with the paracentral lobule. If this area of the brain were involved, it is likely that there would be paralysis and a Babinski sign. I think the edema results from injury to the anterior part of the precentral area, that which Fulton called the premotor area, which has to do with vasomotor phenomena.

Lesions of the Cauda Equina Caused by Rupture of Intervertebral Disk. DR. ADRIEN VERBRUGGHEN.

Effects of Implantation of Methylcholanthrene in the Brain of a Dog. DR. PERCIVAL BAILEY, DR. KENTARO SHIMIZU and DR. EDWARD W. DAVIS.

This paper has been published elsewhere (*J. Neuropath. & Exper. Neurol.* **3**:184-188 [April] 1944).

Treatment of the Convulsive State at the Illinois Security Hospital. DR. A. J. ARIEFF.

This is a preliminary report on the therapy of the convulsive state in a series of 21 patients at the Illinois Security Hospital.

The convulsive state was associated with a psychosis in 8 patients, 4 of whom had paranoid states with deterioration and 4 schizophrenia; 2 patients were mentally defective; 6 patients had organic disease of the brain (in 1, due to trauma; in 1, to encephalitis; in 1, to meningovascular syphilis, and in 3, to chronic alcoholism); 4 had conditions classified as confusional states, and 1 had a constitutional psychopathic state. Deterioration was evident clinically in 11 of these patients, or approximately 50 per cent. Ideas of persecution were common in the whole group because of confusion and lack of insight.

All the 21 patients had major seizures. Fifteen patients also had minor and equivalent states. The ages ranged from 24 to 73 years, with a median of 41. The average stay in the institution was nine years, with a range of from one to thirty-two years. The frequency of seizures varied from two to one hundred a month.

Patients were observed only over a period of six months. Six patients had a remission of all seizures for from three to six months. All but 1 of these patients showed coincidental improvement in behavior. Twelve patients showed improvement in that 4 had remissions of two months and the seizures of all decreased in number up to 90 per cent of the number occurring previously. The symptoms of the actual psychosis remained unchanged.

In 1 patient therapy seemed to have little effect. Practically all the patients presented behavior problems. The behavior of 2 patients was considered good, and that of 17 of the 21 patients was improved. The behavior was unchanged in 2 patients. This evaluation of the behavior was determined by interviewing the attendants in the wards. A decrease in the confusional incidents was likely to result in more cooperative behavior.

Five patients were treated with phenobarbital alone. Three were treated with diphenylhydantoin sodium and phenobarbital; 8, with sodium bromide and phenobarbital; 3 with diphenylhydantoin sodium and sodium bromide, and 2 with the combination of bromide, phenobarbital and diphenylhydantoin sodium. One received a proprietary tablet containing belladonna alkaloids in addition to phenobarbital. With 3 patients treatment with diphenylhydantoin sodium was discontinued after it was found ineffective. This drug did not have any superior effects in relieving disturbances of behavior.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

LEO H. BARTEMEIER, M.D., *President, in the Chair*

Regular Meeting, Sept. 28, 1944

Psychiatry and Demobilization. DR. GEORGE H. PRESTON, Baltimore.

If one thinks from a psychiatric point of view about what happens when armies are disbanded, it is obvious that the term "demobilization" fails to describe the process adequately. Men do not become immobile when they leave the army. They are supposed to begin living again. From a military point of view the army stops moving and is demobilized. From the civilian point of view men who were demobilized by the army must get going again, must be remobilized.

Remobilization in this sense has psychiatric implications. Healthy development is a continuous process,

† Dr. Ziegler died Jan. 8, 1945.

in which the solution of each day's problems rests on the accumulated traces of past experience. The measure of adequacy of mental health is the extent to which past experience provides the individual with skills and defenses suited to the demands of the culture in which he lives. If this continuous process is broken or if the step by step development is twisted so that one step does not prepare for the next, he may find himself confronted, at some point in his life, with a barrier he cannot reach over, avoid or charge through. Military training introduces two disturbing factors: interruption of the orderly day by day process by which suitable civilian experience is acquired, and the introduction of much experience totally unsuitable for civilian life. The time in the man's life at which interruption occurs is of vital importance. It is from this point of view that the problems created by military training and return to civilian life are important.

The problem before us today is the remobilizing of men whose orderly process of development has been interrupted. The stage of development which the man had reached at the time the interruption occurred is of importance. The problem rests more heavily on the younger men, who have not yet attained full adult independence and responsibility, and its seriousness probably varies in intensity as one moves from the agricultural through the mechanical trades groups toward the men in the white collar jobs and the professions. When men return to civil life, it is obvious that they will be thrown more or less suddenly into situations which they expect to find familiar but which, because of changes within themselves, will seem strange. The frustration which results from such unfamiliarity is well known to all psychiatrists. If that were the only factor with which psychiatry will have to deal, the problem would not be so complicated. Unfortunately, other elements enter the picture. Among these are resentment, which often exists in military service, and the effect of living in the closely knit units which are necessary to military routine.

In demobilization this country must deal with several million young men who have become adult without having had time to learn adult responsibility in a socializing situation, landing in a strange and frustrated situation, trained to belong to closely knit units and filled with the experience of destroying any one who does not belong. This is the problem which this country must face and to which the psychiatrist must be ready to make his contribution. If efforts are not successful in breaking down these close-knit, resentful, bewildered groups, it is obvious to any psychiatrist that the compromises and the give and take necessary for a democratic government will be almost unobtainable. It will require wise planning and prompt execution to prevent serious results. These are matters with which psychiatric organizations all over the country should be deeply concerned.

Book Reviews

Personal Mental Hygiene. By Dom Thomas Verner Moore, M.D. Price, $4. Pp. 331. New York: Grune & Stratton, Inc., 1944.

Psychiatrists returning from the military camps and war zones tell of a new source of referral of psychiatric cases—the chaplain. The psychiatrist who was accustomed to receive his clientele largely from exhausted families, bewildered employers and exasperated internists now becomes aware of a new orientation in reporting to or consulting with this new referring agency—the religious branch of the armed forces. Indeed, the mentally ill soldier, sailor or aviator is likely to turn for aid either to the post chaplain or the hospital psychiatrist or to both.

The appearance of Father Thomas V. Moore's "Personal Mental Hygiene" is therefore particularly welcome at this time. It is a book on the preventive aspect of psychiatry written by a man with a distinctly religious philosophy of life. The combination of priest and psychiatrist, while rare in this day and age, is by no means contradictory. The priest has long been functioning in a psychiatric capacity, and the office psychiatrist, consciously or unconsciously, assumes a pastoral role.

However, the combination is also not without its inherent difficulties. These could be summarized as the dangers of "colored judgment" and of "sitting in judgment." The author deals with both problems with variable degrees of success, but with much sincerity and ardor. He frankly asserts that he is devoted to his Roman Catholic Church and does not apologize for having chosen his axioms from its theology. The only thing that one has a right to expect in such a situation is the attitude expressed in a conciliatory letter from one chaplain to his colleague. "Let's stop quarreling," he writes, "it isn't good for the morale of our men. I have arrived at the conclusion that I am perfectly willing to let you serve the Lord in your way, as long as I serve Him in His way."

As for the attitude of sitting in judgment on the patient, instead of the noncondemning relationship of present day psychiatry, the author may be said to have achieved a large measure of success. The style of the book is in many places rather sermonic, but rarely "preachy." The scolding and the hortatory form makes room for the religious teacher's power of illustration. The book offers not only psychiatric expositions but a worth while cultural experience. The author chose the poet's insight into the dynamics of personality as a short cut to analytic understanding. Thus, Oliver Goldsmith is presented as a case of the "creative psychopathic personality," and there follow Rossetti, Swinburne, Francis Thompson and Joyce Kilmer as universal psychologic types.

The book treats of a great variety of subjects: religious scrupulosity, aggressiveness and depression, the rejected and the overprotected child, and the specter of divorce constantly threatening the integrity of the modern family. There is a very readable chapter on the "enjoyment" of prejudices in race hatred; and in the perennial problem of freedom or discipline in school, St. Anselm is shown to be a forerunner of Pestalozzi. However, there are three outstanding aspects of the book which lend it much distinctiveness, namely: (1) the interplay of intellect and emotion in life; (2) the author's attitude toward psychoanalysis, and (3) the positive values of religious sublimation.

The author takes up cudgels for a greater role in psychiatry of ideologies, principled goals and habits of thinking. These he feels (and he is by no means alone in his contention) have been sadly neglected in understanding or helping the neurotic and paranoid personalities. The author was brought up on St. Anselm and Thomas Aquinas and the other great representatives of scholasticism. He is enamoured of the intellectual life. However, he makes a distinction between the form of reasoning, of syllogism and logic, on the one hand, and the major premises, on the other. The reason that these attain to the dignity of axioms is because they have their roots in the bedrock of the emotional life. But then, again, strong emphasis is placed on the distinction between mere animal emotion, which is largely sensational, and the human emotions, which have their indissoluble intellectual connections.

His attitude toward psychoanalysis may be said to be ambivalent. He is at least on speaking terms with the "unconscious" (especially in dream interpretation) and uses a fair number of psychoanalytic terms and principles in explaining the causation of mental conflict. However, he reserves the right to explain in terms of his own philosophy the miracle of the transition from defense mechanisms to the heights of sublimation.

The most constructive aspect of the book is of course the delineation of the domain of religious psychotherapy. This type of therapy, the author asserts, is infinitely more than the retailing of the "milk of human kindness." It requires the exploration and mobilization of basic tendencies and concepts of the personality in meeting particular life situations. He rejects vehemently the conception of religion as an obsessional neurosis on a universal scale. Such an idea of religion he feels is not only therapeutically barren but philosophically inadequate. He insists with warm conviction that religious psychotherapy is indispensable in man's acceptance of his limited roles in society and the universe and the extension of his "time horizons of success" (to use a term of Schilder's), and therefore must become the basis of a psychology of goals and values differentiating mere pleasure from the totality of happiness.

How to Influence Yourself. By K. Morlan, Ph.D. Price, $2.50. Pp. 237. East Chatham, N. Y.: Berkshire Press, 1944.

Every so often a theatrical critic feels it necessary to discuss the question whether or not reviews would be better written by persons who are not specialists in their field, since the viewpoint of the person who sees play after play tends to become warped and the value of his opinion to the ordinary theatergoer thereby diminished. A similar question arises here, when a psychiatrist has to review a book which is written primarily for laymen. Would not a person for whom this book is intended be in a better position to say whether it could help him? A book of this sort is bound to appear naive to the specialist, and the latter

could quite easily look down his nose at it. There is, however, some reason for the psychiatrist to venture an opinion, since he is frequently asked by patients what they could read that might clarify things for them. It is with this idea in mind that I find some justification for my review.

The author is the dean of men and teaches mental hygiene at the Polytechnic Institute of Puerto Rico. Throughout, one has the impression of a humane person, who has seen and heard a great deal and who is imparting the results of his observations in the form of "common sense" rules of living. The tendency of people writing books of this sort is to talk down to the reader, telling him dogmatically that this is what he should do and this is what he should not do to attain full adjustment. Although the author slips into this error rather frequently, there is still enough open-mindedness not to make the book as obnoxious as such books can sometimes be. Throughout, the author refers to interesting case histories and illustrates his material with numerous examples. Many of the current psychiatric viewpoints are represented rather accurately in simple, everyday language, so that in a general way the ordinary layman is oriented correctly. Whether this will help him particularly is another question. Perhaps a person suffering from superficial personality difficulties will find something in this book to help him, but I doubt whether the patient with a full blown neurosis will get anything out of it. It is known that the mere intellectual awareness and knowledge of a problem does not necessarily lead to cure. The value of this book lies mostly in the fact that the reader's attention is called to the possibility that he can do something about his problem even if it is not as simple as would appear to be suggested by the author.

Poet Physicians: An Anthology of Medical Poetry Written by Physicians. Compiled by Mary Lou McDonough. Price, $5. Pp. xiii, plus 210, with index and bibliography. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Most medical poetry is doggerel written for amusement and recreation by busy doctors. However, once in a while an inspired physician produces a poem that can rank with the best of the lyric poetry of his generation. The medical man will view these efforts with greater interest than he will those of men who have had medical training but who are known chiefly as poets, such as Keats and Goldsmith. McDonough has selected the best from the large number of poems available and has included brief sketches of the lives of both living and dead, from many countries.

Old favorites, like "The Chambered Nautilus" and "In Flanders Fields," rub elbows with poems by doctors about doctors. Actually, doctors in the main do not make very good poets. There is a fatalistic, elegiac character about their verse. Death is a natural preoccupation, but many of the poems represent a looking back on life with the philosophy but without the freshness of long acquaintance. Medical poets are old, or at least they sing in the words of old men. Curiously, no woman's name is found in the bibliography of over 400 names. It is difficult to compare living poet-physicians, like Tucker and Moore, with those of a bygone age, like Fracastoro, and even the Elizabethan poet-physicians. There were giants in those days, but they spoke in different idiom. Somehow, the power of verse to evoke images is used to better effect by some of our contemporaries than by those who have gone before. The compiler has spared the reader from *vers libre,* from long poems and from doggerel, for which she is to be thanked. However, in the lyric poetry presented there is almost too great preoccupation with death. There is a solemnity about many of the poems that probably belies the vigorous character of their authors. Humor is often toned with the macaber. The book is elegantly printed on paper that will not reflect the light from the bedside lamp. Many physicians, poets or not, will rejoice in this delightful collection of the inspirations of their colleagues, living and dead. And some may be led to postpone no longer their own efforts to put on paper the results of their own profound thinking.

News and Comment

CANCELLATION OF ANNUAL MEETING OF AMERICAN NEUROLOGICAL ASSOCIATION

The meeting of the American Neurological Association which was scheduled to be held this year has been canceled because of failure to receive permission for the holding of the meeting.

CORRECTION

In the article by Dr. M. J. Madonick and Dr. Ignaz W. Oljenick entitled "Displacement of the Pineal Gland with Extradural Hemorrhage," in the April issue (ARCH. NEUROL. & PSYCHIAT. **53**:311, 1945), the second sentence in the first paragraph, second column, should read:

"The pineal gland was displaced 1 cm. to the right of the midline, 1 cm. posteriorly and 0.5 cm. downward (figure, *B*), according to the method of Vastine and Kinney."

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DISTURBANCES IN SLEEP MECHANISM: A CLINICO-PATHOLOGIC STUDY

I. LESIONS AT THE CORTICAL LEVEL

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Disturbances in sleep consisting of insomnia or hypersomnia can be divided into three main groups: those associated with lesions of the nervous system, those caused by use of drugs and those of psychogenic origin. In this presentation we shall be concerned essentially with hypersomnia caused by lesions of the central nervous system. Although this topic has been the subject of numerous contributions, the material under observation justifies a revaluation of this interesting problem. Attempts to explain the mechanism concerned in disturbances of sleep in man on a neuroanatomic and physiologic basis have led to various interpretations. The problem is beset with difficulties because the lesions in many of our cases and in those reported by other investigators were neither single nor limited to specific areas in the nervous system. This is especially true when the somnolence is associated with cerebrovascular lesions or diseases with bilateral or multiple lesions of the central nervous system. It is not always possible to state with certainty that a localized lesion due to a neoplasm is the cause of this physiologic deviation because there may be a widespread disturbance in function through compression of other structures or through interference with the cerebrospinal circulation. A careful evaluation, however, of the clinical symptoms and the location of the significant lesion may aid in proving which centers and pathways are responsible for hypersomnia or insomnia.

From the Neuropsychiatric Service and the Neuropathological Laboratory of the Montefiore Hospital, and the Neurological Department of Columbia University College of Physicians and Surgeons.

Presented before the Chicago Neurological Society on May 20, 1943 (preliminary report) and before the New York Academy of Medicine, Section of Neurology and Psychiatry, Feb. 8, 1944. An abstract of the paper with discussion appeared in the January 1945 issue of the ARCHIVES, page 79.

As will be demonstrated, disturbances in sleep may occur with lesions at various levels of the nervous system, from the cortex to the medulla oblongata.

There is some experimental evidence in the human subject indicating the probable site of the responsible lesion. Disturbances of sleep in patients with involvement of the hypothalamus, either by neoplasm or secondary to encephalitis lethargica, indicates the importance of this center. Although the hypothalamus seems to be the main center controlling sleep, it is well to remember that it is in intimate connection with the cortex, the thalamus, the basal ganglia, the mesencephalon and the brain stem. A lesion in any of these centers or in the connecting pathways may result in disturbance of integration of the sleep mechanism. The disintegration of this mechanism may be caused by destructive and irritative lesions, as well as by psychogenic factors. The disturbances of a psychologic nature may also depend on interference with the centers and pathways, to be described. In several of the cases included in this presentation there were slight psychotic or neurotic phenomena. Despite their presence, psychologic and neurologic examinations showed that the disturbance of sleep was organic in nature.

From the nosologic point of view, disturbances in sleep should include the various common designations: lethargy, somnolence, stupor, coma and unconscious states. Some observers believe these to be separate entities rather than phases or stages of the same dysfunction, regulated by identical centers and pathways. They assert that hypersomnia or somnolence should be differentiated from stupor, for in the former the patient can easily be aroused and when awakened appears to be in complete possession of his senses. Some observers claim that encephalitic patients when awakened are promptly oriented and that

their consciousness appears unclouded. Others maintain, however, that somnolence or lethargy, as best seen in cases of encephalitis, varies from slight drowsiness to complete stupor. Our experience and the observations of many other investigators indicate that in a number of cases of encephalitis the patients cannot be aroused completely from their lethargy. Disturbances of sleep and consciousness leading to stupor, coma and other unconscious states are probably closely related. They are the result of lesions in those parts of the central nervous system concerned with the sleep mechanism. A lesion in these centers or in their connections may disturb not only sleep but consciousness. It is therefore not unusual to find in such cases not only pure pathologic sleep but a certain amount of stupor and coma. The analysis of our material does not justify clearcut differentiation of sleep, unconscious states, stupor and coma.

About 300 cases of disturbances in the sleep mechanism were observed clinically, and autopsies were performed in 57 cases. Most of the deaths were due to neoplasms; the remainder resulted from vascular or other diseases of the nervous system. The 57 cases in which autopsy was performed and the 2 cases in which the diagnosis was verified at operation and which were included in this presentation were studied fully in order to determine the location of the lesion. A number of cases in which diffuse lesions existed in the cortex, diencephalon, mesencephalon and metencephalon were omitted from this presentation, for their inclusion would have been confusing from the point of view of localization.

Location of Lesions	No. of Cases
Cortical	9
Corticodiencephalic	25
Diencephalic (hypothalamus)	17
Mesencephalic-metencephalic	8
	59

METHOD OF PROCEDURE

Every patient reported on was observed during the period of disturbance of sleep. A number of questions were asked, and attempts were made to arouse the patient, as indicated in the brief history of each case. The few patients in deep coma who could not be aroused were not included in this study. Since many observers believe that such factors as increased intracranial pressure, endocrine disturbances and ocular manifestations play an important part in disturbances of sleep, special attention was given to these features in order to evaluate their significance. Only the pertinent facts regarding disturbances in sleep will be given in the report of these cases.

Each brain was sectioned coronally or horizontally at intervals of 1 cm., so that lesions of significant size were not missed. In all instances blocks from the areas of destruction or of the tumor, and from the tissue above and below them, were embedded in pyroxylin and stained by the myelin sheath and the cresyl violet method. In many cases entire sections of the brain were embedded in pyroxylin and cut serially at a thickness of 50 microns. The hypothalamic region was studied by the same methods in all cases.

LESIONS AT THE CORTICAL LEVEL

The ability of man to fall asleep voluntarily is an indication that the sleep mechanism is under the regulation of higher cortical centers. It is therefore reasonable to assume that disturbances of cortical function have some influence on abnormal sleep. The awakening of a patient from lethargy and mental cloudiness, as seen in cases of lethargic encephalitis and other diseases of the central nervous system, and his response to questions are further evidence that the higher psychic centers play an important role in the regulation of sleep. The cases of psychogenic sleep furnish additional proof of cortical influence on sleep. Psychogenic disturbances in sleep, which probably have their origin in the cortex, are most likely mediated by way of the corticohypothalamic pathways. In our cases in which lesions existed at the cortical level, we postulate that involvement of the aforementioned centers or tracts removed the normal regulatory control of the cortex over the hypothalamus.

This report is concerned with 9 cases of disturbances of sleep in which the lesion was entirely restricted to the cerebral cortex and white matter.

REPORT OF CASES

CASE 1.—*Infrafrontal meningioma: somnolence and unconsciousness. No clinical evidence of increased intracranial pressure.*

G. C., a woman aged 80, had sudden onset of paralysis of the left side, associated with somnolence, followed by unconsciousness, from which she could be aroused. Later she regained consciousness and began to move the paralyzed extremity.

Neurologic Examination.—Examination disclosed diminished reflexes bilaterally, absence of pathologic reflexes, loss of vision and secondary optic nerve atrophy in the right eye. The patient was dull and apathetic, with periods of somnolence.

Laboratory Data.—The urine and blood chemistry were normal. Lumbar puncture was not performed.

Autopsy.—There was a large, encapsulated meningioma situated between the two frontal convolutions, destroying the greater part of the white matter of all the frontal convolutions and leaving only a thin shell of gray matter (fig. 1). The tumor did not extend posteriorly beyond the tips of the anterior horns of the lateral ventricles. The diencephalon was not compressed, and the hypothalamic nerve cells stained normally.

The tumor in this instance did not compress the hypothalamus. The loss of vision in the right eye was the result of compression of the right optic nerve.

CASE 2.—*Chondrosarcoma of the right frontal convolutions: somnolence and, toward the end, semistupor. Evidence of increased intracranial pressure.*

G. S., a boy aged 13 years, gave a history of projectile vomiting, followed shortly by diplopia and headache. Thereafter he became drowsy but could be aroused.

Neurologic Examination.—Examination at this time revealed an abnormal amount of hair; large genitalia and an undescended left testicle; large head, hands and feet, and scoliosis. There were anosmia, bilateral papilledema, with secondary optic nerve atrophy, and weakness of the right side of the face of central type. The presence of a pinealoma was suspected, and roentgen therapy was instituted.

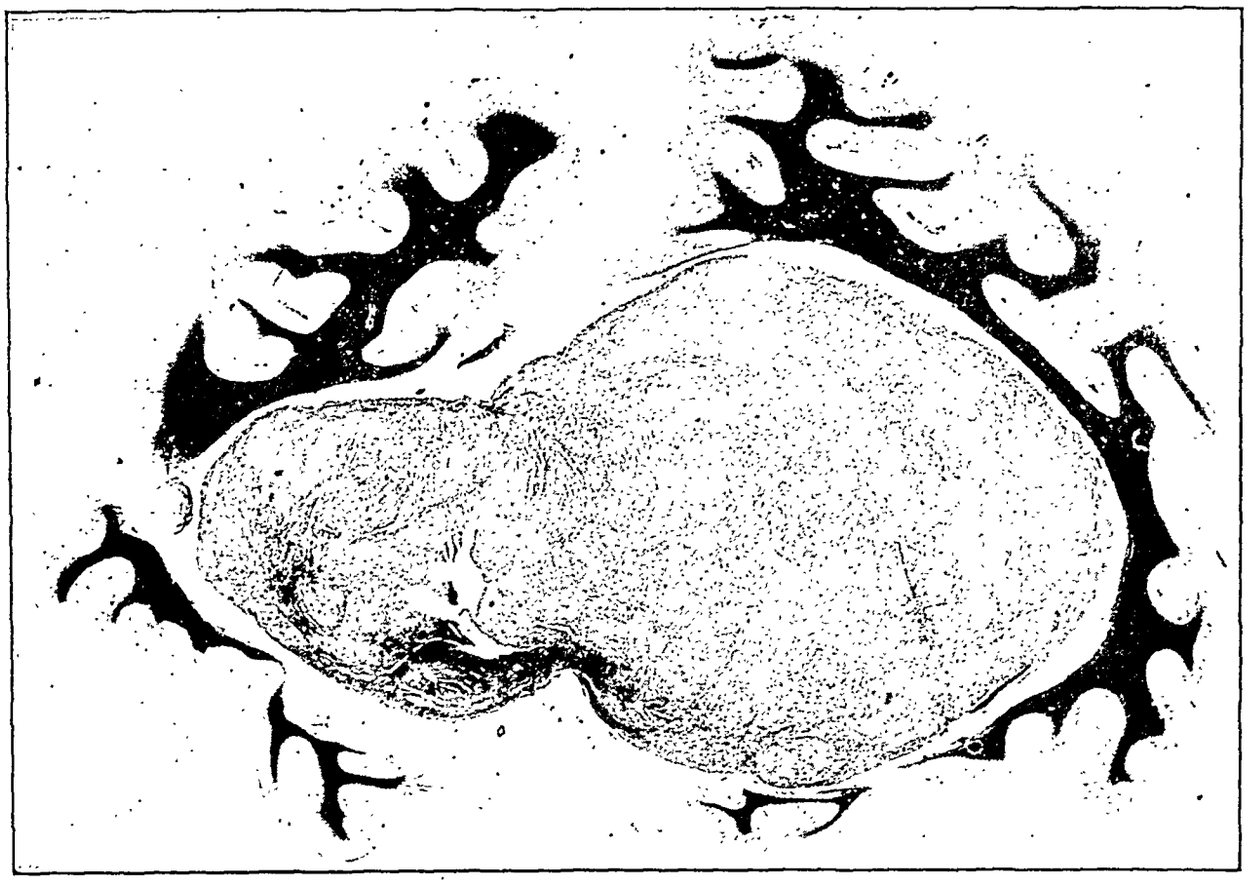

Fig. 1 (case 1).—Infrafrontal meningioma.

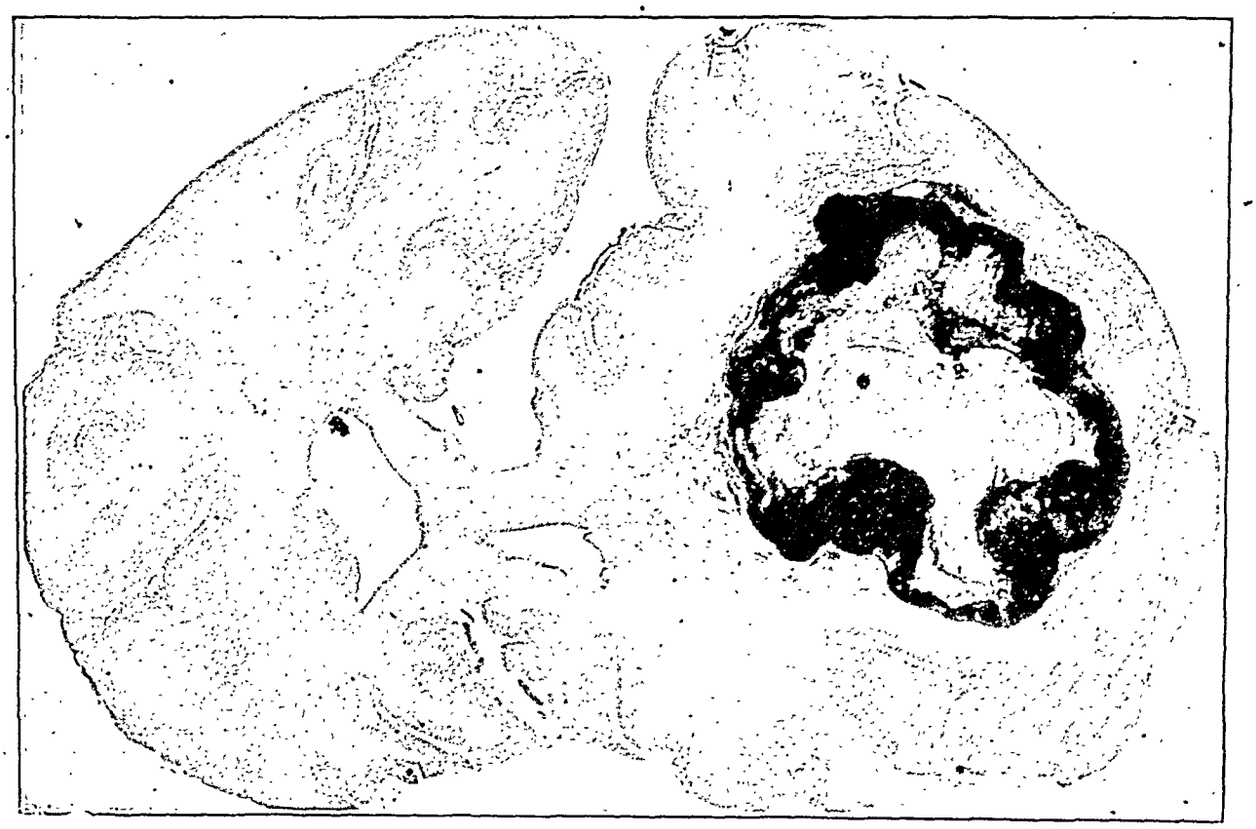

Fig. 2 (case 2).—Chondrosarcoma of the right frontal convolutions. Notice compression and distortion of the tip of the right lateral ventricle.

Laboratory Data.—The spinal fluid was under an initial pressure of 400 mm. of water; it was clear and contained 3 cells per cubic millimeter.

Course.—After roentgen therapy the drowsiness disappeared; the patient became well adjusted, attended

school at the hospital and entertained himself by listening to recordings of many of the classics in literature. Two years later there developed a hard mass in the right frontal bone, aspiration of which revealed a chondrosarcoma. The boy became increasingly drowsy and somnolent. In the early stages he could easily be aroused when he was loudly spoken to or prodded. The drowsiness increased to semistupor. Spinal puncture at this time showed an initial pressure of 440 mm. of water.

Autopsy.—There was a large cauliflower mass, measuring 4.5 by 3.5 cm., in the dura over the right frontal convolutions. The frontal and motor convolutions were compressed by this neoplasm (fig. 2). Part of the second and third frontal convolutions of the right side were destroyed and infiltrated by the tumor. The nerve cells of the various hypothalamic nuclei did not show pathologic changes.

The lesion in this instance was essentially cortical (frontal). Of interest is the disappearance of the lethargy after high voltage roentgen therapy. Interference with hypothalamic function can be ruled out, for pathologic changes could not be demonstrated in the hypothalamus. The presence of diplopia in this case, alone of the group with cortical lesions, may have been the result of the increased intracranial pressure.

CASE 3.—*Meningiomas compressing the right frontal convolutions; somnolence; mental impairment. Evidence of increased intracranial pressure. Removal of tumor and disappearance of somnolence and other symptoms.*

L. Y., a woman aged 43, complained of increasingly severe headaches, somnolence and weakness.

Neurologic Examination.—There were bilateral papilledema and drowsiness, from which the patient could be aroused. There was marked impairment of memory, with considerable disorientation and blocking of thought.

Laboratory Data.—The spinal fluid showed an initial pressure of 230 mm. of water. There was a trace of albumin and globulin, and the total protein content was 43 mg. per hundred cubic centimeters. The urine and blood chemistry were normal. Ventriculographic studies suggested an expanding lesion of the right frontal region.

Course.—Craniotomy was performed, and two small meningiomas over the right frontal convolutions were removed. After the operation the somnolence disappeared. The patient remained well about five years after operation.

The evidence that the patient recovered from the somnolence after removal of the meningiomas from the frontal convolutions indicates that this cortical area plays a role in the control of the sleep mechanism.

CASE 4.—*Hemangioma compressing the right frontal convolutions; lethargy. No evidence of increased intracranial pressure.*

C. S., a woman aged 60, complained of headache and drowsiness, which progressed to lethargy.

Neurologic Examination.—The patient was continuously drowsy but could be awakened at times. Sometimes she lapsed into deep stupor. There was no papilledema or other abnormal neurologic sign.

Laboratory Data.—The blood chemistry was normal. The cerebrospinal fluid was under a pressure of 130 mm. of water; the total protein content was 25 mg. per hundred cubic centimeters.

Autopsy.—There were multiple telangiectatic hemangiomas of the liver, the frontal bones and the vertebral bodies. In the right frontal bone a circular area, 3 cm. in diameter, blue-black, compressed the frontal convolutions. The hypothalamic nuclei and their nerve cells were normal.

CASE 5.—*Subdural hematoma compressing the left frontal convolutions; lethargy ending in coma. No increase in intracranial pressure.*

G. J., a boy aged 15 years, suffered from drowsiness, from which he could be awakened.

The only neurologic findings were hyperreflexia and a Babinski sign on the right side. Later the patient became comatose and could not be aroused. Before his death, the left pupil became larger than the right, and both were fixed to light.

Laboratory Data.—A spinal tap revealed xanthochromic fluid, with an initial pressure of 140 mm. of water.

Autopsy.—There was thickening of the dura, with a subdural hematoma on the left side compressing the frontal, motor and temporal convolutions. The pia-arachnoid was slightly adherent and thickened. The anterior horn of the left lateral ventricle was constricted, distorted and pushed to the right. The hypothalamic nuclei and their nerve cells were normal.

In this case the drowsiness, ending in coma, undoubtedly was caused by the compression of the left hemisphere, especially the frontal convolutions. Except for the slight distortion in the anterior horn of the left lateral ventricle, there was no evidence of increased intracranial tension.

CASE 6.—*Glioblastoma multiforme of the right cerebral hemisphere, extending from the frontal to the occipital convolutions, slightly compressing, but not invading, the superior part of the diencephalon; lethargy. No evidence of increased intracranial pressure.*

S. A., a man aged 59, gave a history of "dozing off" at frequent intervals.

Neurologic Examination.—There was left hemiplegia with signs of injury to the pyramidal tract and loss of all forms of sensation on the left side. The fundi were normal. The patient fell asleep frequently during the examination but could easily be awakened when spoken to loudly or shaken. When awakened, he would answer questions properly. At times he was confused and disoriented. This mental state was most pronounced when he was lethargic but would clear up if he was awakened or, interestingly, if a pretty nurse assisted in the examination.

Laboratory Data.—All examinations, including urinalysis, gave essentially normal results. The urea nitrogen of the blood measured 25 mg. per hundred cubic centimeters. The cerebrospinal fluid was under a pressure of 200 mm. of water, but the patient was straining at the time. The total protein content of the fluid was 67 mg. per hundred cubic centimeters; the cell count was normal. The Wassermann reaction was negative.

Autopsy.—There was a glioblastoma multiforme of the right hemisphere extending from the frontal to the occipital convolutions, including the gyrus cingulus on the right side and part of the corpus callosum on the left side (fig. 3). The right lateral ventricle was distorted and constricted. The hypothalamus was not invaded, but the superior part on the right side was slightly compressed (fig. 3). Sections through various

Fig. 3 (case 6).—Glioblastoma multiforme of the right hemisphere, extending from the frontal to the occipital convolutions and including the gyrus cingulus. Notice the slight compression of the right lateral ventricle and the superior part of the right hypothalamus, with absence of invasion.

regions of the hypothalamus did not disclose any pathologic changes in its nerve cells.

The tumor in this case was essentially limited to the cortex, with slight compression of the superior part of the right hypothalamus. However, there were no changes in the hypothalamic nerve cells. There was no significant evidence of increased intracranial pressure, either clinically or pathologically. The initial pressure of 200 mm. of water was the result of poor relaxation of the patient, which, according to Friedman and Merritt [1] and others, may be disregarded. In this instance, the right gyrus cingulus was also invaded by the neoplasm. This area, as suggested by Papez,[2] plays some role in emotional disturbances and may also be concerned with the function of sleep.

CASE 7.—*Spongioblastoma polare of the left motor and parietal region; somnolence. Clinical evidence of slight increase in intracranial pressure.*

S. H., a woman aged 60 had spontaneous pain in the right upper extremity, dizziness, nausea and vomiting, paralysis of the right upper and lower extremities and aphasia.

Neurologic Examination.—Examination disclosed hemiparesis with pathologic reflexes and a hemisensory syndrome on the right side, bitemporal pallor of the optic disk, psychomotor retardation and depression. In the last two months of her illness the patient slept most of the time. She was not able to speak but answered questions by gestures when awakened.

Laboratory Data.—The blood chemistry was normal. The cerebrospinal fluid was under a pressure of 110 mm. of water. The reaction for globulin was 1 plus, and the total protein content of the spinal fluid was 62 mg. per hundred cubic centimeters.

Autopsy.—There was a spongioblastoma polare in the left motor and parietal regions. It extended slightly into the centrum ovale. The hypothalamus was not compressed, and the hypothalamic nuclei did not show any pathologic changes.

The disturbance of sleep in this case was the result of involvement of the cortex, as there were no changes in the hypothalamus. Although the spinal fluid pressure was normal, the changes in the optic disks were considered to be secondary to increased intracranial pressure.

CASE 8.—*Meningioma of the right parieto-occipital convolutions, with peculiar disturbances of sleep. Clinical evidence of increased intracranial pressure. Questionable compression of the hypothalamus, without pathologic changes.*

R. S., a woman aged 48, sustained an injury to the back of her head during a fall. One year later she complained of failing vision, weakness and headaches. At this time she began to have peculiar disturbances of sleep. She would go to sleep about 6 p. m., awaken at 2 a. m., fall asleep again within an hour and then reawaken at 7 a. m. Soon afterward she would fall asleep again and sleep a great part of the day. She could easily be aroused but would soon lapse into sleep again.

Neurologic Examination.—Examination revealed a large mass over the right occipital bone, bilateral papilledema with suggestive left homonymous hemianopsia and conjugate deviation of the head and eyes to the right. There was hyperreflexia on the left side. The patient was confused and rambled continuously when awakened, until she fell asleep again.

Laboratory Data.—Roentgenographic examination of the skull disclosed a circumscribed area of destruction of bone in the right occipital and parietal regions the size of a lemon, with radiating spicules of ossification. The urea nitrogen of the blood was normal. The cerebrospinal fluid was under a pressure of 115 mm. of water; the fluid was clear and contained no cells.

Course.—The extracranial and intracranial portions of the tumor were removed at two separate operations. The tumor extended to the sagittal suture and compressed the opposite occipital lobe. The patient went into shock and died.

Autopsy.—Part of the bone in the righ parieto-occipital region was destroyed by the invading meningioma. The tumor was situated over the right parieto-occipital lobes, causing extensive destruction of the superior parietal, the angular and part of the first occipital convolution and compressing the occipital convolutions on the opposite side. The ventricles on the right side were constricted and distorted. There was questionable compression of the diencephalic nuclei, but the nerve cells of the hypothalamus appeared normal.

This case is of interest because of the peculiarity in the disturbance of sleep in which the patient slept a great part of the day and had short periods of awakening. Although the cerebrospinal fluid pressure was within normal limits, the papilledema and the constriction of the ventricular system indicated increased intracranial pressure.

CASE 9.—*Pachymeningitis hemorrhagica interna, compressing the right frontoparietal convolutions; somnolence. No evidence of increased intracranial pressure.*

F. J., a man aged 49, complained of headache, weakness, hiccuping, yawning and drowsiness. When he was drowsy, and sitting, his head would sag and turn to the right, and he would fall asleep. When awakened he would answer questions coherently for a short time and then promptly fall asleep again. Thirty years previously he had had a syphilitic infection, for which he received treatment. There was no history of head injury or of alcoholism.

Neurologic Examination.—The patient was extremely somnolent and yawned frequently; there was spastic hemiparesis with pyramidal tract signs on the left side; the pupils were irregular, and the left one was fixed to light and in accommodation; there was no papilledema. The patient exhibited mental deterioration and poor orientation.

Laboratory Data.—The Wassermann reactions of the blood and the spinal fluid were 4 plus. The cerebrospinal fluid was under a pressure of 80 mm. of water. The urine was normal, and the urea nitrogen of the blood was within normal limits.

Course.—The patient became progressively more drowsy, lapsed into coma and died. The temperature ranged between 97 and 98 F. for four weeks, and once it was 96.4 F.

1. Friedman, A. P., and Merritt, H. H.: Personal communication to the authors.

2. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

Autopsy.—The outer surface of the dura over the right frontomotor and parietal region was extensively thickened and contained an organized hematoma. The right frontal, motor and parietal convolutions were flattened. There was a slight constriction of the right lateral ventricle. Sections of the dura disclosed a typical picture of pachymeningitis hemorrhagica interna. There was a slight meningeal reaction. No inflammatory process was noted in the cortex. The hypothalamus was not compressed, and its nerve cells were normal.

The somnolence in this case was caused by compression of the right frontal, motor and parietal convolutions.

COMMENT

Experimentally there is little evidence that pure cortical lesions cause disturbances in the sleep mechanism, although Sager [3] and Neiwenhuyzen [4] produced catalepsy in the cat after decortication. Johnson [5] spoke of special "sleep" neurons in the cerebral cortex since sleep shows the patterns of learning by experience and habit formation and these features are characteristic of cortical activities. According to him, catabolic products activate the sleep neurons, which inhibit the other cortical neurons. He stated the belief that "the relations between the sleep system and the whole of the central nervous system, concerned only in elaborating the reactions of the waking state, are mutually antagonistic."

Pathologic sleep, chiefly in the form of hypersomnia, had been known to occur in cases of pure cortical neoplasms. In some of these cases it was difficult to rule out the role played by secondary compression of the hypothalamus and the effect of the generalized increase in intracranial pressure. It is well to bear in mind that a neoplasm, no matter how small, will interfere to some degree with the circulation of the cerebrospinal fluid. Righetti,[6] in 1903, analyzed the histories of 775 patients with tumors of the central nervous system. Of these, 115 had pathologic sleep. In 6 per cent of the latter the neoplasms were situated in the frontal lobe. Léchelle, Alajouanine and Thévenard [7] reported 2 cases of tumor of the frontal lobe, with hypersomnia as the main symptom in 1 case and as the only symptom in the other. They asserted that somnolence is the predominant symptom of tumors of the frontal lobe. Kolodny [8] investigated 38 cases of tumors of the temporal lobe and found hypersomnia in 9. Frazier,[9] in a collection of 105 cases of tumors of the frontal lobe, noted some form of hypersomnia, ranging from drowsiness to stupor, in 34. He regarded somnolence as a neighborhood symptom and as secondary to involvement of the diencephalon. He stated the opinion that sleepiness may be due to increased intracranial pressure, within the third ventricle particularly. McKendree and Feinier [10] analyzed 100 cases of cerebral neoplasms and found somnolence most constantly when there was pronounced internal hydrocephalus. The absence of somnolence in many other cases of pure cortical lesions with evidences of increased intracranial pressure militates against the view that increased intracranial tension may cause or be the sole basis of disturbances in the waking center or centers. It seems likely that the role played by increased intracranial pressure in dysfunction of sleep is somewhat overestimated. In a review of 328 cases of tumors of the central nervous system in which necropsy was performed, evidence of increased intracranial pressure was present in about 70 per cent; yet disturbances of sleep occurred only in 18 per cent. The percentage of cases of increased intracranial pressure in our series of cases of disturbances of sleep was also about 70 per cent.

Of about 60 cases of pathologic sleep associated with a lesion of the central nervous system, a solitary cortical lesion was found in 9. In none of these cases was the hypothalamus invaded; in 2 instances compression of the hypothalamus could not be completely ruled out. In 5 cases (1, 4, 5, 6 and 9) there was no clinical or manometric evidence of increased intracranial pressure. In 4 cases (2, 3, 7 and 8) there was increased intracranial pressure, and the role played by this factor in dysfunction of sleep cannot be absolutely ruled out. In case 1 manometric studies were not done, but there was no clinical evidence for increased intracranial tension. In cases 7 and 8 the manometric readings were normal, but there was clinical evidence of increased intracranial tension. The

3. Sager, O.: Experimentelle Untersuchungen über die Bulbocapninstarre, Ztschr. f. d. ges. exper. Med. **81:** 543, 1932.

4. Niewenhuyzen, F. J.: Etude sur la localisation des phénomènes cataleptiques chez le chat, Acta brev. Neerland. **4:**89, 1934.

5. Johnson, G. T.: Sleep as a Specialized Function, J. Abnorm. & Social Psychol. **18:**88, 1923.

6. Righetti, R.: Contributo clinico ed anatomopatologica alla studio die gliomi cerebrali, Riv. di pat. nerv. **8:**24, 1903.

7. Léchelle, Alajouanine and Thévenard: Deux cas de tumeur du lobe frontal à forme somnolente, Bull. et mém. Soc. méd. d. hôp. de Paris **49:**1347, 1925.

8. Kolodny, A.: The Symptomatology of Tumors of the Temporal Lobe, Brain **51:**385, 1928.

9. Frazier, C. H.: Tumors Involving the Frontal Lobe Alone, Arch. Neurol. & Psychiat. **35:**525 (March) 1936.

10. McKendree, C. A., and Feinier, L.: Somnolence, Arch. Neurol. & Psychiat. **17:**44 (Jan.) 1927.

most definite criteria for clinical evidence of increased intracranial tension considered by us were papilledema and projectile vomiting; all other symptoms are questionable. Manometric evidence of increased intracranial tension consisted of an initial pressure of 200 mm. or above with the patient relaxed and in the lateral recumbent position. Diplopia was present in only 1 case. There were no endocrine disturbances, except in a boy of 13 (case 2), in whom the presence of a pinealoma was suspected and who had an abnormal amount of hair, large genitalia and large hands and feet. Slight deviations from the normal temperature were present only in case 9. In 1 case the removal of a meningioma from the right frontal area resulted in disappearance of the somnolence.

From our series of cases of pure cortical lesions, and from the cases reported by other authors, we are of the opinion that some fibers for the control of sleep may originate in the cerebral cortex, especially the hippocampal, cingular, frontal, premotor and temporal lobes. Bard's [11] experiments on sham rage indicate that the hypothalamus is to some degree under the control of the cerebral cortex. These impulses, such as occur in affective states for the expression of emotion and feelings (Davison and Kelman [12] and others), are mediated by voluntary and involuntary pathways, probably controlled by the corticohypothalamic pathways. The voluntary efferent impulses are possibly mediated via the pyramidal pathways. This subject will be discussed in greater detail in a subsequent presentation.

Somnolence is infrequently observed in cases of pure cortical lesions, except when these are fairly extensive, because the neurons and pathways controlling sleep are widely scattered and are not concentrated in one small area, as are the same structures in the hypothalamus. It is well known that a complete hemiplegia is more likely to occur with a small lesion of the internal capsule than with a small cortical lesion. Similarly, disturbances in sleep are more likely to occur as a result of hypothalamic than of cortical lesions.

Cranial trauma may also lead to total loss of consciousness or to lethargy. In some instances the patient can be awakened; in others, not. These cases cannot be cited as proof of cortical control, for in most instances there was interference with cerebrospinal pressure; moreover, the lesions were usually widespread and probably involved the hypothalamus.

SUMMARY AND CONCLUSIONS

In 9 cases pathologic sleep was associated with lesions in the cortex. In none was there invasion of the hypothalamus. In 2 cases compression of the hypothalamus could not be completely ruled out. On microscopic examination, however, there was no evidence of changes in the nerve cells.

Increased intracranial pressure was present in only 4 of the 9 cases. It is reasonable to assume that the role played by increased intracranial tension in dysfunction of sleep is negligible, if not totally insignificant. Ocular and endocrine disturbances, except for diplopia in 1 case and endocrine features in another, were absent in this group of cases.

From the study of this series of cortical lesions, we are of the opinion that some fibers for the control of sleep originate in the cerebral cortex, especially the hippocampal, cingular, frontal, premotor and temporal convolutions. These areas are connected with the hypothalamus by means of the corticohypothalamic pathways. Injury to these areas or to their connections with the hypothalamus is occasionally the cause of pathologic sleep.

Montefiore Hospital for Chronic Diseases.

11. Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

12. Davison, C., and Kelman, H.: Pathological Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595 (Oct.) 1939.

DENIAL OF BLINDNESS BY PATIENTS WITH CEREBRAL DISEASE

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Occasional cases of denial of blindness or deafness in cases of focal cerebral disease have been reported in the French, Russian and German literature but have received hardly any attention from Anglo-Saxon authors. However, denial of blindness in cases of pathologic conditions of the brain is frequent, although overlooked by most observers. Here, 6 cases of denial of blindness will be reported, the literature reviewed and the syndrome discussed.

REVIEW OF LITERATURE

In 1896 Anton gave a verbal report of a case with bilateral softenings of the visual radiations, followed by complete blindness which the patient himself did not notice. Anton wrote two papers,[1] in which he reported this case and 3 others. The first case was that of a 56 year old seamstress who was amaurotic but unaware of her blindness. She had dysphasia of the amnestic type; otherwise the results of neurologic examination were essentially normal. She did not appear to be very deteriorated. Spatial orientation was impaired, and she was unable to localize voices or to estimate distances by hearing. Autopsy revealed bilaterally symmetric lesions of the angular gyrus and the first and second occipital gyri, involving the medullary substance, and a small lesion in the splenium of the corpus callosum. The second case was that of a 64 year old teamster who was completely deaf but thought he could hear well. The patient often complained that others made such a noise that he could not follow the conversation. It appeared as though he had auditory hallucinations but he never answered questions or expected answers to his own questions. He was friendly and seemed oriented. He had dyslexia and dysgraphia. The results of neurologic examination were otherwise normal. There was no marked deterioration. Later paranoid delusions developed. No autopsy is reported. The clinical diagnosis was bilateral softening of the temporal lobes. The third case was that of a 69 year old female dairy worker who was admitted in a state of excitement and confusion with sensory aphasia. The patient was unaware of her inability to understand spoken words. Autopsy revealed bilateral destruction of the first and second temporal gyri, extending toward the occipital lobes. Anton stressed the destruction of the association fibers between the occipital, temporal and lower parietal lobes. He concluded that the syndrome of denial of sensory deficiency due to cerebral lesions is caused by destruction of the association tracts. He described clearly that such a syndrome is not due to deterioration, hallucinations or hysterical manifestations. Actually, only his first case constitutes what later was referred to as Anton's syndrome.

Careful combing of the literature revealed that the syndrome had been described before Anton, but only in a casual manner, usually with stress on other features of the case. Von Monakow[2] described 2 cases. The first was that of a 70 year old man with left hemiplegia and slight aphasic disturbances. The patient was not greatly deteriorated. He was blind but was unaware of his blindness. Often he thought that he was in a dark hall. Autopsy showed old and recent bilateral softenings in the cuneus and the lingular gyrus, extensive areas of encephalomalacia of the left occipital lobe and both superior temporal gyri and softenings in the right thalamus and the right lateral geniculate body. The second case was that of a 50 year old man with epileptic seizures in whom bilateral hemianopsia developed. He had amnestic aphasia and was disoriented. Spatial orientation and memory for the appearance of objects were impaired. He was totally unaware of his blindness. Autopsy showed recent bilateral

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1. Anton, G.: (*a*) Ueber die Selbstwahrnehmung der Herderkrankungen des Gehirns durch den Kranken bei Rindenblindheit und Rindentaubheit, Arch. f. Psychiat. **32:** 86-127, 1899; (*b*) Ueber Herderkrankungen des Gehirns, welche vom Patienten selbst nicht wahrgenommen werden, Wien. klin. Wchnschr. **11:**227-229, 1898.

2. von Monakow, A.: Experimentelle und pathologisch-anatomische Untersuchungen über die Beziehungen der sogennanten Sehspäre zu den infracorticalen Opticuscentren und zum Nervus opticus, Arch. f. Psychiat. **16:** 151-199, 1885.

softenings of the cuneus and the lingular gyrus and old softenings in the third frontal gyrus. Dejerine and Vialet [3] reported the case of a 64 year old man who had two apoplectic attacks, the second followed by complete and sudden blindness. The patient walked like a blind man but did not realize his blindness; he called objects by false names and said tears were in his eyes. Autopsy showed an area of old encephalomalacia in the cuneus and lingular gyrus on the right side, extending toward the occipital pole, and fresh softenings of the calcarine and the lingular gyrus on the left side. Rossolimo [4] reported the case of a patient who was totally blind and did not recognize it. Autopsy revealed a softening in the cuneus and the lobus lingualis on the left side involving most of the white matter. There was a massive hemorrhage of the basal ganglia on the right side. Mayer [5] reported a case of a 64 year old man who had visual hallucinations and did not admit his blindness. Bilateral softenings of the medial surfaces of the occipital lobes were found. Lunz [6] described a case of complete blindness in which the fundi and pupils were normal; the patient was not aware of his defect. Bilateral occipital softenings were found. Bonhoeffer [7] described a patient with alexia who was not aware of his inability to read. Lejoune, Raymond and Galezowski [8] reported the case of a 57 year old man with pseudobulbar palsy; the patient recovered from the first attack of blindness, which he noted, but was unaware of his second attack; autopsy was not performed. Probst [9] reported the case of a 62 year old man who had a cerebral accident followed by hemianopsia at the age of 56, became aphasic and confused at 57 and had right hemiplegia, dysarthria and cortical blindness at 58. He remained indifferent toward his blindness and thought that he was in a dark cellar most of the time. An extensive, butterfly-shaped glioma filling large parts of both hemispheres and softening of both occipital lobes were found.

In 1908 E. Redlich and Bonvicini [10] published careful observations on 3 patients with Anton's syndrome. The case of a fourth was published in a subsequent paper. The first patient, a 21 year old man, was admitted with epileptic attacks and headaches. He was temporarily confused, disoriented and euphoric. He had defects of memory and retention but was not grossly deteriorated. He had no aphasia or apraxia. He was totally blind; his pupils did not react to light, and the disks were choked. He was absolutely unaware of his blindness; he thought his vision was intact. A tumor in the region of the septum pellucidum involving both sides of the centrum semiovale and the heads of both caudate nuclei was found. No pathologic diagnosis was made. The second case was that of a 49 year old woman who had right hemiparesis and mild aphasic disturbances and within eight months became totally blind. Neurologic examination revealed bilateral optic neuritis. The pupils were wide and did not react to light. There was slight right hemiparesis, and the deep tendon reflexes were more active on the right side than on the left. The Babinski sign was present bilaterally. There was slight amnestic aphasia and no apraxia; tactile recognition was normal. The patient was forgetful of events of the recent past; she was disoriented for date and place but did not show any gross deterioration. She confabulated about her vision, though she was totally blind; usually she said it was dark, and she used all kinds of alibis if she failed to identify objects correctly. Her recall of colors and forms from memory was good. She usually populated her environment with various persons from earlier life. Autopsy revealed an endothelioma the size of an egg which arose from the clivus and compressed half of the pons and the cerebellum. The third, seventh and eighth nerves on the left side showed compression atrophy; there were secondary optic nerve atrophy and internal hydrocephalus. The third case was that of a 72 year old janitor who was admitted to the psychiatric clinic. Nine months before his admission headaches and left homonymous hemianopsia developed. Five days before his admission right hemianopsia developed, and he became totally blind. He complained about darkness, asked "for light," was unable to identify

3. Dejerine and Vialet: Sur un cas de cécité corticale, Compt. rend. Soc. de biol. **11**:983-997, 1893.

4. Rossolimo, G.: Ueber Hemianopsie und einseitige Ophthalmoplegie vasculären Ursprungs, Neurol. Centralbl. **15**:626-637, 1896.

5. Mayer, C.: Eine doppelseitige homonyme Hemianopie mit Orientierungstörungen, Monatschr. f. Psychiat. u. Neurol. **8**:440-462, 1900.

6. Lunz, C.: Zwei Fälle von korticaler Seelenblindheit, Deutsche med. Wchnschr. **1**:381-393, 1897.

7. Bonhoeffer, K.: Casuistische Beiträge zur Aphasielehre, Arch. f. Psychiat. **37**:564-597, 1903.

8. Lejoune, Raymond and Galezowski: Cécité corticale par double hemianopie, Rev. neurol. **19**:680-691, 1906.

9. Probst: Ueber einen Fall vollständiger Rindenblindheit und vollständiger Amnesie, Monatschr. f. Psychiat. u. Neurol. **9**:5-21, 1901.

10. Redlich, E., and Bonvicini, G.: Weitere klinisiche und anatomische Mitteilungen über das Fehlen der Wahrnehmung der eigenen Blindheit bei Hirnkrankheiten, Neurol. Centralbl. **30**: 227 and 301, 1911; Ueber das Fehlen der Wahrnehmung der eigenen Blindheit bei Hirnkrankheiten, Jahrb. f. Psychiat. **29**: 1-134, 1908.

objects and recognized people only by their voices. He never admitted his blindness. The patient exhibited no aphasic difficulties but had pronounced dysgraphia. He showed mild deterioration and had slight defects of memory for remote and recent events; he was able to repeat only four digits. His optic recall for numbers and forms was normal. Neurologic examination revealed slight spastic hemiparesis and hemihypesthesia on the right side. The pupils and fundi were normal. The patient died, and the autopsy revealed thrombosis of both occipital arteries and extensive softenings of the mesial and basal parts of the occipital lobes. The uncus, hippocampus, visual radiations and fornix showed extensive softenings.

The fourth case was that of a 64 year old man who was admitted with weakness of the right arm and right hemianopsia after a cerebral accident. In a second accident the patient became totally blind. He was not aware of this blindness and did not admit it at any time. He confabulated constantly and showed slight impairment of intelligence. He was rather attentive, but his memory for recent and remote events and his retention were very poor. His spatial orientation was badly impaired.

Redlich and Bonvicini drew attention to the fact that the syndrome is not rare; in most cases observed there is bilateral hemianopsia. In the majority of cases there are lesions of the occipital lobe, but the syndrome occurs in cases of generalized disease of the brain with blindness. Deterioration alone does not explain the syndrome.

Albrecht,[11] Anton's pupil, described 3 cases. In the first, a 53 year old colonel had slowly progressing spastic hemiplegia on the right side. He had bilateral papilledema and was completely blind. His pupils were fixed to light. He always complained of darkness but never admitted to being blind. At first he showed only slight intellectual deterioration. Later on he became confused and hallucinated. Autopsy revealed hypernephroma of the right kidney and a metastatic lesion, the size of an egg, in the left parietal region and another in the cerebellum. The second case was that of a 41 year old laborer who was admitted with complaints of headache, dizziness, lack of critical ability and difficulties in the naming of objects. Both disks were choked, and the patient had left hemiplegia, left analgesia and astereognosis. Four months later he became comatose and was completely blind when he recovered from the episode. He thought, however, that he was able to see. Autopsy showed a sarcoma of the posterior part of the right thalamus, extending into the lateral ventricle. The third case was that of a 31 year old business man who had headaches, right hemiparesis and complete blindness. He was hypomanic and euphoric; at times he had delusions of persecution and became rapidly confused. He was rather deteriorated and showed considerable impairment of memory. He had atrophy of both optic nerves and spastic hemiparesis of the right extremities. He believed that everything was dark, used constant subterfuges in regard to his lacking eyesight and stated that he could see perfectly well. Autopsy revealed a tumor of the left frontal lobe, the size of a man's fist. Albrecht maintained Anton's theory that the syndrome is due to an interruption of neural conduction between remote cortical areas in different lobes. When association tracts are interrupted, the lack of sensory stimulation due to blindness or deafness is no longer perceived.

Poetzl[12] described disturbances of perception in cases of left hemiplegia and discussed the lack of perception of blindness. He stressed the frequency of the syndrome, particularly among patients with dementia paralytica with optic nerve atrophy. He was the first one to emphasize that the syndrome of anosognosia, a term coined by Babinski,[13] may be due to two lesions, one in the thalamus and the other in the parietal cortex, or to one subcortical parietal lesion. Tunero[14] described a patient with a tumor in the right pulvinar the size of a goose egg who presented Anton's syndrome. Weber[15] described the case of a patient with two consecutive cerebral accidents in the course of bacterial endocarditis; the second accident was followed by blindness, which he denied. Raney and Nielsen[16] reported briefly 2 cases of denial of blindness. The first was that of a 47 year old man with complete loss of vision, left hemiplegia and left homonymous hemianopsia. The patient claimed he could see objects on both sides, although he named objects incorrectly on the left side. The

11. Albrecht, O.: Drei Fälle mit Antons Symptom, Arch. f. Psychiat. **59**:883-941, 1918.

12. Poetzl, O.: Ueber Störungen der Selbstwahrnehmung bei linkseitiger Hemiplegie, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**: 117-168, 1924.

13. Babinski, M. J.: Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie), Rev. neurol. **27**:845-848, 1914.

14. Tunero, J.: Ein Fall mit Antons Symptom, Psychiat. et neurol. japon. **41**:679-690, 1931.

15. Weber, F. P.: Agnosia of Hemiplegia and of Blindness After Cerebral Embolism, Lancet **1**:44-46, 1942.

16. Raney, A. A., and Nielsen, J. M.: Denial of Blindness (Anton's Symptom), Bull. Los Angeles Neurol. Soc. **7**: 150-151, 1942.

other case was that of a 54 year old woman who was completely blind; she could not distinguish daylight from darkness but described objects. No autopsy was done.

REPORT OF PRESENT CASES

CASE 1.—M. T., a 49 year old white American housewife, was admitted to the New Haven Hospital on July 9, 1943. Four years before her admission the patient first noted double vision, which disappeared when she changed her glasses. In the spring of 1943 she again noted a decrease in vision; particularly, she felt unable to see from side to side as well as formerly. She began to have headaches, chiefly in the parietal and occipital regions, which were intermittent, rather severe and occurred mostly in the morning. There was also roaring in the left ear. She vomited a few times, without any nausea, and had several attacks of numbness over the right side of her face, which lasted about a minute. The patient complained of some loss of memory for recent events in the months before her admission. The past medical history was not contributory. She came of lower middle class Yankee stock, went through grammar school as far as the eighth grade, had been married for twenty-five years and had twelve children, ranging from 24 to 3 years of age. She worked at home and was apparently well adjusted and contented. There was no history of any severe psychologic problems or of alcoholism. The family history was not contributory.

Physical examination showed obesity and a blood pressure of 170 systolic and 110 diastolic; there were no signs of cardiac decompensation. The pulse rate was 84 and the temperature 98.6 F. Vision was greatly diminished, so that she was unable to read even the largest newspaper print. Examination of the visual fields showed left lower quadrantanopsia. There was bilateral papilledema, of 4 D. The pupils were about 6 mm. in diameter; they were round and regular, did not respond to light but reacted in convergence. There were no objective findings pertaining to the fifth nerve. Hearing was not impaired objectively. The cranial nerves were otherwise normal The left palpebral fissure was narrower than the right.

Strength, coordination and muscular tone of the trunk and the extremities were normal. The sensory status was normal. The abdominal reflexes were present on both sides. All deep tendon reflexes were hyperactive and equal on the two sides. The plantar responses were diminished.

Laboratory Data.—The urine was normal. The Kahn reaction of the blood was negative. The blood count showed 20 Gm. of hemoglobin per hundred cubic centimeters, 4,140,000 red cells, 5,400 white cells and a normal differential count. The nonprotein nitrogen measured 33 mg. per hundred cubic centimeters. An electroencephalogram was normal. A roentgenogram of the skull revealed increased convolutional atrophy and enlargement and erosion of the sella turcica, probably secondary to increased intracranial pressure. The diagnostic impression was tumor of the brain stem or of the hypothalamus.

Ventriculographic examination, on July 15, pointed to a midline tumor of the midbrain, resulting in elevation of the floor of the third ventricle, with a complete block at the origin of the aqueduct of Sylvius and obstructive hydrocephalus. The roentgenologist thought that the tumor might be a pinealoma. On July 26 a craniotomy in the right parietal area was performed by one of us (J. F. D.), the splenium of the corpus callosum split and the third ventricle entered, but no tumor could be found in the region of the pineal gland, the hypothalamus or the midbrain. The patient's immediate postoperative course was uneventful. However, on August 9 she became confused and agitated; she was completely disoriented and was euphoric; she seemed to hear voices of persons she knew, saw members of her family, though they were not present, and talked at random. It appeared at that time that the patient was completely blind but seemed to disregard her blindness. When asked how many persons were present in her room, she would guess wrong, and she gave completely false descriptions of persons and objects in her room and of the examiner. When a light was flashed directly in front of her eyes, she was unable to say when the light was on or off. When her blindness was pointed out to her, she would reply, "Oh. I see all right. It's quite dark, but I see you." There was evidence of intellectual deterioration. The patient was only roughly oriented for current events and showed but little knowledge of topics of common interest, such as the war, prices and rationing. She was unable to define differences between a river and a lake or a midget and a child, or to make statements about similarities of an orange and a banana or a buggy and an automobile. She would not cooperate even in the simplest calculation. There was evidence of an amnestic aphasia. She seemed to have severe defects in her memory of recent events and could not remember that she had been operated on. She was unable to retain the examiner's name, even for three minutes. She did not know that she was in the hospital and thought she was at home. There was no astereognosis. On August 30 a suboccipital craniotomy (by Dr. Bernard Brody) was carried out and no tumor was found. The immediate postoperative course again was good, but gradually the patient showed advanced deterioration. She lay motionless in her bed, would not talk, became incontinent and had to be fed. The neurologic signs did not change materially except that secondary optic nerve atrophy developed. The patient remained in the hospital in a vegetating condition until Jan. 8, 1944, when she was taken home for economic reasons.

The diagnosis remained unclear; the presence of a hypothalamic tumor was unverified, and the question of an obstruction of the sylvian aqueduct, of unknown cause, arose.

CASE 2.—J. C., an 8 year old white boy, was admitted to the New Haven Hospital on Oct. 2, 1943, with the complaint of blindness.

Four years before his admission he had an acute attack of otitis media of the left ear; thereafter the ear drained intermittently. In August 1943 his tonsils and adenoids were removed, and shortly afterward "boils" developed in the canal of the left ear. During the first week of September he complained of pain in the left eye, the left shoulder and the left side of the neck. At this time he was given "vitamin B_1 for toxic neuritis." Fifteen days before admission to the hospital he "went blind." Three days later he had a stiff neck and was treated for meningitis at another hospital. Nine days before his admission a mastoidectomy was done on the left side. Cultures showed Staphylococcus albus. After the operation he was given a transfusion and appeared to be doing well until the day before his admission, when he began to vomit. Examination of his eyegrounds showed papilledema. He was referred to this hospital for admission.

The family and the past history were noncontributory.

Physical Examination.—The boy was pale and appeared chronically ill; he was alert and talkative.

There was a bandage over the left ear. The right pupil measured 4 mm. and the left 3.5 mm. The right pupil did not react to light. The left pupil showed minimal contraction to light, and light shined into this eye caused consensual contraction of the right pupil. He was unable to see light when a flashlight was shined directly into the right eye. On the left side he could recognize light only in the temporal field. The fundi showed choking of the disks, measuring 4 D.; the vessels were extremely tortuous. There was inability to turn the left eye to the left beyond the midline or to turn that eye down and out. Otherwise the cranial nerves were intact. The neck was rather stiff. The extremities were equally strong on the two sides. Motor coordination was good. Sensations for touch, pinprick and position were intact. All deep reflexes were absent; the plantar response was diminished on the right side and equivocal on the left. Numbers written in his hands were recognized. When he was given objects to name, he called a safety pin a "big pen" or a "straight pen." Calculations were poorly done; $2 \times 3 = 7$ and $4 \times 3 = 7$. When asked to multiply 6 by 9 and to add 9 and 14, he replied, "Can't do." When he was asked to touch his left hand to his right shoulder, he put his left hand on his right elbow. When asked to touch his right hand to his right ear, he touched his left hand to his right ear. When given a pen and asked to write, he wrote his name and address and wrote to simple dictation. He could feed himself with a fork and a spoon. The clinical impression was that of an abscess of the superior part of the left temporal lobe.

On Oct. 4, 1943, during a ventriculographic study, the wall of an abscess was encountered 3 cm. below the burr hole in the left occipital area. The left ventricle could not be tapped. The right ventricle and the third ventricle were shifted to the right. Operation was performed on the same day by one of us, J. F. D. An incision was made anterior to the left ear; after removal of some of the bone, the dura was opened, and the wall of an abscess was encountered at a depth of 0.75 cm. Fifty cubic centimeters of thick, yellow, putrid pus welled forth. A second, large, connecting cavity was found posteriorly. Iodized poppyseed oil was instilled into the depths of the cavity, which was then packed with petrolatum gauze after a Penrose drain had been inserted.

Postoperative roentgenograms showed the iodized oil to be "approximately 3 cm. from the inner table of the temporal bone in the frontal view, while in the lateral view it appeared to be above the tip of the mastoid." On the day after the operation the pupils no longer reacted to light or consensually. Moreover, when a flashlight was shined directly into either eye, the patient was unable to tell whether the light was on or off. At this time he maintained that his vision was good; he described his physician as wearing a hat, although actually none was worn. He made similar mistakes in other tests. When asked to point to the window or the door, he would point in various directions. When his errors were explained to him, he still would not admit that he was blind. When asked whether he could see, he said he could see well. When he was told to look at objects and to name them, he made wrong guesses. When his mistakes were pointed out to him, he did not seem surprised and insisted that his eyesight was good. When told directly that he could not see, he again retorted that he could see well. This behavior persisted two more days. On October 8, when his vision was tested with a flashlight, he could not tell whether the light was on or off; and when he was asked whether he was not blind, he said "I don't care if I can't see." To most questions involving vision he replied "I don't know."

On October 11 he could tell for the first time when a light was shined onto either the nasal or the temporal field of the left eye. There still was no pupillary response to light. A small fungus developed in the wound, but by October 30 the fungus was pulsating. On November 28 the right eye was blind. The left pupil measured 4 mm., the same as the right; the left pupil reacted to light and the right consensually. The patient still had trouble in remembering the sequence of the months and the correct order of words in his prayers. He was unable to state when Christmas is, nor did he know how many weeks or days there are in a month. Calculations were done as before: $4 \times 3 = 7$, and $4 \times 2 = 6$. He identified objects placed in either hand. The wound in the head was completely healed by December 5, and he was discharged on that date. Thereafter he continued to do well; and when he was seen on January 11, vision had improved so that he was able to count fingers at 3 inches (7.6 cm.) with his left eye and was aware of the blindness of the right eye. He still omitted four months when asked to name the months of the year in order. He did calculations correctly: $7 + 5 = 12$; $4 \times 3 = 12$; $6 \times 4 = 24$; $15 - 7 = 8$. He readily obeyed complicated commands pertaining to the body scheme.

CASE 3.—A. J., a white man aged 46, a machinist, was admitted to the New Haven Hospital on Oct. 3, 1943, complaining of blurred vision in his right eye of three weeks' duration.

Present Illness.—Three and a half weeks before entry to the hospital, while working, he felt a sharp pain in the right eye and thought that a particle had got into the eye. There was no redness or watering, and the pain subsided in about a half-hour, to recur intermittently thereafter. Three days later, while inspecting a finished product with a magnifying ocular, he noted that he could see nothing with the right eye. When he closed the left eye, he realized that the right eye was completely blind except for "hazy vision" in the upper field. He could not see objects directly ahead or below him. He also noted sharp pain on movement of the eye to either side and a sense of pressure behind the eye. About the same time there were intermittent "sharp pains deep in the bones" of the right cheek and temple and the right side of the forehead. These lasted from a few minutes to two or three hours and usually were relieved by acetylsalicylic acid.

One week before his entry there was blurring of vision in the left eye, which increased in intensity so that on admission he was able to read only headline type in the newspapers. For three days prior to admission he had had a chest cold.

The family and the past medical history were not contributory.

Physical Examination.—The patient was well developed, stocky and slightly obese. He did not appear to be in distress. General physical examination revealed nothing remarkable. The temperature was 98.6 F., the blood pressure 128 systolic and 104 diastolic, the pulse rate 76 and the respiratory rate 12 a minute. The head was symmetric. There was hyperesthesia to light touch, but not to pain or to deep pressure, over the cheek, the periorbital region, the forehead, the temple and the parietal region on the right side. The right pupil was 4 mm. and the left 3 mm. in diameter. The right pupil reacted sluggishly to light; the left, promptly. Extraocular movements were full; there was no nystagmus. There was pronounced concentric constriction of the visual field of the left eye. Determination of the field

of the right eye was not possible. There was bilateral choking of the disks, measuring 3 D. In the upper third of the left disk was a small perivascular area of brown-red pigmentation, which appeared to be an old hemorrhage. Otherwise the cranial nerves were normal. Muscular strength was good in all extremities. The knee and ankle jerks were livelier on the right side than on the left. Associated movements on walking were more noticeable on the left side than on the right. The finger to nose test was not as well done on the right side as on the left.

Laboratory Data.—The blood count showed 4,800,000 red cells, hemoglobin 88 per cent and 9,600 white cells. The Kahn reaction of the blood was negative. Urinalysis revealed a specific gravity of 1.007, no albumin and no sugar. Microscopic examination showed no cells or casts. Roentgenograms of the skull revealed the right optic foramen to be slightly larger than the left. The cortical outline was thinner on the right side. Lumbar puncture revealed an initial pressure of 350 mm.; after 12 cc. of clear, colorless spinal fluid was withdrawn, the final pressure was 180 mm. The fluid contained 28 lymphocytes and 8 polymorphonuclear cells per cubic millimeter; the total protein was 510 mg. per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative, and the colloidal gold curve was 0000000000.

Three days later there was slight flattening of the nasolabial fold on the left.. The corneal reflexes were now absent bilaterally. A ventriculogram was made on October 16. The ventricular fluid did not appear to be under tension, and 40 cc. of fluid was removed. However, the filling was unsatisfactory. The roentgenograms showed subdural air over the right hemisphere and slight dilatation of the anterior horns.

After ventriculographic examination there was rapid reduction of the remaining vision in the right eye, so that determination of the visual fields on October 21 showed complete loss of vision of the right eye and visual acuity of 6/100 in the left eye, with some constriction of the upper temporal field in the left eye. Five days later there was further constriction of the superior and temporal fields in the left eye, vision in that eye now being 1/40—2. Since the ventriculograms failed to show any evidence of an expanding lesion, the patient was discharged from the hospital on November 3. He was readmitted on November 17 because during the two weeks he had been away there had been complete loss of vision in the left eye, and he was now completely blind. He had also noticed "dizziness" on standing or sitting up quickly. Physical examination showed that the pupils were small, measuring 2 mm., and did not react to light; the disks were about the same as before, and, while the extraocular movements were still full, there was now fine sustained nystagmus on extreme lateral gaze to the right or to the left. Two days later the nystagmus was more pronounced to the right. The right disk was whiter than the left; both were swollen, the left more than the right. On November 24 a pneumoencephalogram was made. Again, there was poor filling, and the films were of no diagnostic value. Ventriculographic examination was repeated on November 26, and this time irregularity of the wall and the floor of the right anterior horn was seen. There was incomplete filling of the anterior portion of the third ventricle. An electroencephalogram taken on December 2 showed a focus of slow waves in the right frontotemporal area.

After the second ventriculographic examination the patient began to have intermittent elevation of temperature, sometimes reaching 101 F. He was disoriented for time and place. He said that he could see; but when he was asked whether a light was shined in his eyes, he made numerous errors and could not point out the position of the light. He described the suit that the physician wore, calling it brown, when actually it was white. He could not point to either the window or the door of his room. The patient was obviously blind but did not seem to notice this himself. When it was explained to him, he refused to believe it. He attempted to reach for objects, and when given them, tried to handle them as though he could see. At times he had difficulty in naming the objects he handled.

By December 10 the patient responded only in mumbles, appeared stuporous, refused to eat and had to be fed with a tube. He preferred to lie with his head and eyes turned to the right, and forcible turning of the head to the left caused him to moan with pain. The neck was stiff; Kernig's sign was present bilaterally, and the plantar response was equivocal on the left and diminished on the right. The next day he was comatose. On December 12 the temperature, which had gone progressively higher on the three preceding days, reached 105 F. The pulse rate was 120 and the respiratory rate 60. He was cyanotic; the distal extremities were cold, and he died the same day.

Anatomic Study (Dr. Hildegard Arnold).—There was a small cerebellar pressure cone. The right optic nerve was thickened by an inherent tumor, so that the nerve appeared to be about three times its normal diameter. The tumor involved the entire floor of the third ventricle and was adherent to it. The pituitary body was normal. There was a firm, slightly hemorrhagic mass filling the whole of the third ventricle and replacing most of the hypothalamic structures. The growth had extended in plaques to involve the orbital gyri of both frontal lobes.

Anatomic Diagnosis.—The diagnosis was primary sarcoma involving the optic chiasm and the tuber cinereum, with flattening of cerebral gyri.

CASE 4.—J. C., a Russian Jew aged 62, was admitted to the psychiatric clinic on April 19, 1944, with symptoms of anxiety, depression and agitation, after several abortive attempts at suicide. In the summer of 1943 the patient, after some domestic worries, became run down. She lost weight, could not sleep and complained of constant burning in her stomach. A diagnosis of "leukemia" was made, and the patient was treated with liver and pentnucleotide until the blood picture became normal again. Two weeks before admission she became tense, agitated and anxious, slashed her wrist and swallowed a piece of wood. She moaned and complained constantly and was admitted to the psychiatric clinic.

Her medical history was not contributory. The menopause occurred at the age of 52. The patient had six children, all of them highstrung but physically well. She had been born in Russia and had come to the United States at the age of 17 years. She had been a fairly well adjusted, outgoing, hard working, aggressive woman, who held the family together and had been responsible for its social rise.

Physical Examination.—The physical status was normal except for hypertension, with a pressure of 170 systolic and 98 diastolic, slight enlargement of the heart, accentuation of the aortic second sound and a soft, blowing apical and pulmonic diastolic murmur. The electrocardiogram showed an axis shift characteristic of hypertrophy of the left ventricle. The rest of the physical examination and all laboratory tests (a Kahn test of the serum, studies of the blood and urine, roentgenographic examination of the skull, serial roentgenographic study of the gastrointestinal tract, pyelographic examina-

tion, lumbar puncture, electroencephalographic studies and examination of the stools) gave normal results. Excretion of the dye in the phenolsulfonphthalein test was normal. The nonprotein nitrogen measured 34 mg. per hundred cubic centimeters. The patient continued to be anxious, agitated and depressed; she thought that she was incurably sick and complained constantly of "burning up." Otherwise there were no delusions or hallucinations. There was no evidence of deterioration. The sensorium was clear, and memory and retention were normal.

Treatment consisted of administration of large doses of barbiturates by day and use of paraldehyde and wet packs at night. On April 26, at 8:30 p. m., she complained about dizziness and said she had fallen. Examination at that time revealed nothing significant. At 9:30 p. m. the patient was discovered lying across the bed in an attitude of prostration, with cold, clammy, blue skin and stertorous breathing; the pulse was good, and the blood pressure was 110 systolic and 70 diastolic. The patient was comatose for about half an hour. Neurologic examination revealed nothing significant. When she regained consciousness, she was confused and disoriented and had considerable difficulty in understanding and expressing herself. On the morning following the attack it was noted that the patient did not recognize any objects. She could not say correctly where the door or the windows were, nor how many persons were in the room. She was unable to see strong light in front of her eyes. She made false descriptions of the appearance of persons in the room. It was evident that she was blind and did not perceive her blindness. When asked whether she was blind, she denied it. Her pupils were 5 mm. in diameter; they were equal and regular and reacted to light. Neurologic examination revealed no abnormality except for absence of the abdominal reflexes and a bilateral Babinski response. The retinal vessels appeared extraordinarily thin. During the examination the patient had a second attack, which was almost identical with the one on the previous evening except that it was more severe and of longer duration. She was comatose for about two hours and then gradually recovered consciousness. In this state she had definite jargon aphasia with inability to comprehend. On the following day the aphasia and all pathologic and neurologic signs, including the blindness, has disappeared. The patient seemed much improved mentally and was calm, friendly and cooperative. There were no hypochondriacal complaints. The retinal vessels showed slight arteriosclerosis but were not as thin as during the attack. The patient was oriented; her memory seemed good except for complete amnesia for her attacks. It was as though she had "shocked" herself out of her agitated depression. The nature of these attacks remained unclear. Possibly she had cerebral angiospasm which caused temporary focal symptoms, aphasia and blindness, with Anton's syndrome. One week after the attack the patient was just as psychotic as before and remained so until her discharge to another hospital, on June 20, 1944.

CASE 5.—C. C., a 59 year old woman, was admitted to the New Haven Hospital for the second time on July 3, 1944. Known to be diabetic since 1932, she responded to diet therapy, and use of insulin was unnecessary until 1939. In 1936 she noted deterioration of vision in both eyes, particularly the left. An ophthalmologist found hemorrhages in both retinas. In 1940 vision in her right eye became temporarily worse, and for a short while she was unable to see at all. Her vision improved again for several months and then became gradually poorer. On Sept. 25, 1941 the patient was admitted to the New Haven Hospital for the first time, on account of rapidly failing vision.

Physical examination revealed a blood pressure of 225 systolic and 84 diastolic; otherwise the vital signs were normal. The fundi were obscured by opacities, presumably in the lens. The heart was slightly enlarged to the left. The patient had 4 plus pitting edema of both legs. There is no report of any personality disturbance, and the results of neurologic examination were normal.

Laboratory Data.—The urine gave a 4 plus reaction for albumin and contained sugar. The blood count revealed 3,000,000 red cells, 71 per cent hemoglobin, 5,700 white cells and a normal differential count. The Kahn reaction of the blood was negative. The nonprotein nitrogen of the blood measured 29 mg. per hundred cubic centimeters. The fasting blood sugar level was 149 mg. per hundred cubic centimeters; the serum protein measured 5.56 Gm. per hundred cubic centimeters; the phenolsulfonphthalein test showed excretion of only 11 per cent of the injected dye in four hours. A roentgenogram of the chest showed enlargement of the left ventricle; there was hypertrophic osteoarthritis and calcification in the left upper quadrant of the abdomen, of undetermined cause.

A diagnosis of intercapillary glomerulosclerosis (Newburger and Peters,[17] Kimmelstiel and Wilson[18]) was made. The patient was followed in the metabolism clinic, and treatment with a high protein, antidiabetic diet and small doses of insulin was continued. Under this regimen she was able to hold her own until the spring of 1943, when her eyesight began to fail notably. The nonprotein nitrogen had risen to 52 mg. per hundred cubic centimeters, and an ophthalmologist found numerous punctate opacities in the vitreous and retinal hemorrhages. In the summer of 1943 she was unable to work as supervisor of a boys' camp because of poor vision. On May 10, 1944 it was noted that she was "wandering mentally." At the time of her second admission the physical findings were as follows: The vital signs were normal. The blood pressure was 220 systolic and 110 diastolic. There had been no changes with respect to the heart since her first admission except that she had no edema. For all practical purposes the patient was blind. She had to be fed and taken care of like a blind person. She flinched away from a strong light directly in front of her eyes but was unable to localize the light. The right pupil measured 4 mm. and the left 3 mm.; both reacted promptly but minimally to light. The bulbi seemed tender, and the patient resented examination of the eyes. The ophthalmologist, Dr. E. Blake, saw many large, stringy opacities in the vitreous body of each eye. The retinal vessels were sclerotic, and there were retinal hemorrhages in the right eye. The left fundus could not be seen clearly. The other cranial nerves and the motor system were intact. The patient felt pinprick all over her body; evaluation of her sense of touch, vibration and position was impossible. All the deep reflexes were present and physiologically active except for the absence of ankle jerks. The Babinski sign was present on the left side. Urinary incontinence was noted occasionally.

Laboratory Examinations.—The blood count showed 3.400,000 red cells, 12.5 Gm. of hemoglobin per hundred

17. Newburger, R. A., and Peters, J. P.: Intracapillary Glomerulosclerosis: A Syndrome of Diabetes, Hypertension and Albuminuria, Arch. Int. Med. **64:** 1252-1264 (Dec.) 1939.

18. Kimmelstiel, H., and Wilson, C.: Intracapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12:**83-98, 1936.

cubic centimeters, 9,500 white cells and a normal differential count. The Kahn reaction of the blood was negative. The urine gave 4 plus reactions for albumin and sugar (on admission). The cerebrospinal fluid was under an initial pressure of 200 mm. of water. The total protein content was 51 mg. per hundred cubic centimeters; there were no cells; the colloidal gold curve was 0000000000.

The patient was quiet and cooperated to the best of her ability. She was talkative and answered all questions, though she did not understand the more complex questions. There was no aphasia. She was completely disoriented and thought she was in a religious school. She stated that it was December, though the weather was warm, and said that the year was 1918, 1940 or 1945. Her retention and memory for recent events were highly defective. She had hardly any information about the war except that she knew that the country is at war. She was unable to give her address but could give her name and her husband's name. Her knowledge of the remote past was better. Speech was incoherent and irrelevant and at times almost rambling, with a marked flight of ideas. She seemed rather euphoric and had no idea that she was either mentally or physically ill. Although she was almost amaurotic, she acted and spoke as though she could see well. She described the room, the places of doors and windows and the number, names and appearance of persons, but her statements were false. She was unable to state whether a light in front of her eyes was on. At all times she localized such a light inaccurately. In her confabulations she made detailed but false statements about the occurrences in the room. When asked whether she was blind or did not see well, she made vigorous denials. When told she was blind, she did not acknowledge it. On July 12, 1944 the patient had a cerebral accident without loss of consciousness; left hemiparesis, involving the face and the extremities, was noted. She was unable to move the extremities spontaneously; muscular tone was decreased. The patient reacted to pinprick by withdrawal of the left leg and slight movements of the left arm. No other sensory examination could be carried out. The deep reflexes were slightly more active on the right side than on the left. There were dorsiflexion and withdrawal to plantar stimulation on the left side and plantar flexion on the right. The patient was unaware of her left hemiparesis and even denied its presence when it was pointed out to her. However, she was aware of the existence of her left extremities. Subsequent examinations showed no changes up to the time of her discharge, on Aug. 4, 1944.

CASE 6.—P. K., a white man aged 45, was admitted to the New Haven Hospital for the first time on March 25, 1942. One week before admission he complained of severe frontal headaches and dizziness and became slightly confused. He reported seeing yellow lights on his left side. The past personal history was not contributory. The patient was of Irish-American stock, born and raised in Connecticut; he graduated from high school. For thirteen years he had been a widower. He was a successful manager of a small mattress factory. He had always been a stable, pleasant, outgoing person and had shown no peculiarities or maladjustment in his behavior. There was no indication of any psychopathic trends.

The physical examination gave normal results except for the neuropsychiatric changes to be described. The patient was pleasant, cooperative, conscious and oriented. There was no evidence of intellectual deterioration. Motor speech and comprehension were normal except for occasional difficulties in naming objects. There were noticeable dyslexia and dysgraphia. Right homonymous hemianopsia was present. The fundi showed bilateral papilledema, of 3 D. The pupils were normal. The other cranial nerves and the motor and sensory systems were intact. The reflexes were physiologic. A roentgenogram of the head showed an "asymmetric skull, convolutional atrophy and displacement of the pineal gland to the right." An electroencephalogram revealed "a focus of slow waves in the left temporal lobe." The diagnostic impression was that of a cerebral neoplasm in the left parieto-occipital region. On April 1, 1942, ventriculographic examination and subequent craniotomy were carried out (Dr. W. Klemperer). A soft, fleshy, reddish tumor was found in the subcortical portion of the inferior parietal and posterior temporal region on the left side, extending toward the occipital lobe. A specimen, measuring 6 by 4 by 5 cm., was removed. The histologic diagnosis (Dr. H. Zimmermann) was glioblastoma multiforme.

The patient recovered rapidly; lost his aphasia, dysgraphia, dyslexia and hemianopsia, and was asymptomatic from May to November 1942. In November 1942 he reported two incidents of glassy vision. On Dec. 7, 1942 he had one attack of complete disorientation while driving a car. In January 1943 he experienced three attacks of complete blindness, each lasting several hours. At that time his symptoms of amnestic aphasia reappeared. His memory was impaired. He was unable to write and could barely detect movements of a hand in front of his eyes. The disks showed bilateral choking, of 3 D. On Feb. 11, 1943 a ventriculographic examination and craniotomy on the right side were carried out (Dr. William T. German). It was observed that the tumor had spread through the posterior part of the corpus callosum; a 2.5 cm. specimen of solid tumor was removed by suction from the right occipitoparietal region. The postoperative course was uneventful but the neurologic signs remained unchanged. At that time it was noted that he pretended to see, though he was obviously blind.

On March 19, 1943 the patient was transferred to the psychiatric clinic. He was moderately restless but cooperative, although he finally had to be helped in eating and with care of his body. He knew he was in the New Haven Hospital, but he was unable to remember the operation unless he was reminded of it. Memory for the remote past was fair. He showed pronounced amnestic aphasia and agraphia. He was paranoid toward his family and persistently demanded to be discharged. On all clinical examinations he was completely unable to distinguish strong lights from darkness. The only examination which revealed a trace of vision was the psychogalvanic skin test, carried out by Prof. Donald Marquis. Both disks showed signs of secondary atrophy. The pupils were about 6 mm. in diameter and were equal, round and regular; they reacted promptly and extensively to light and in convergence. The cranial nerves were intact. Muscular strength and tone of the extremities were physiologic. There were bilateral action tremor and past pointing in the finger to nose test and slight ataxia in the heel to shin test. Position sense and vibration sense of the trunk and the extremities were definitely impaired. Touch, temperature and pain senses, topognosis and two point discrimination were normal, as was body perception. There was no finger agnosia. Recognition of materials was good, but recognition of forms was impaired beyond that due to his amnestic difficulty. All deep tendon reflexes were normal. The abdominal and cremasteric reflexes were absent; the plantar reflexes were of flexor type.

His ability to cooperate in formal testing procedures (Dr. Margaret Keller) was extremely limited, owing to his distractability, confusion and aphasia. He showed difficulty in comprehension, which was greater at some

times than at others. In the Binet vocabulary test, which under such circumstances was not very valid, the patient succeeded in defining the average number of words for adults. This was, however, not achieved under standard conditions. Words were repeated for him when necessary, and he was given several trials unless his response indicated that he did not know the word to be defined. On the verbal half of the Wechsler-Bellevue test his performance was extremely inferior. He could answer a few of the questions relating to general information and comprehension but succeeded with only one problem in arithmetic and failed completely in the similarity test, being unable to grasp what was required of him. He showed a notable deficiency in all tests involving memory, repeating only three digits forward and two in reverse with many repetitions and instructions. He could remember only one item from a paragraph immediately after it had been read to him. He frequently forgot the question asked before he was able to complete his answer. It was noticed that his memory improved when distractions were reduced to a minimum during the period of delay preceding recall. The patient showed perseverative tendencies at times. He seemed to become fixed on a certain type of response and to be unable to change unless distracted by some irrelevant stimulus. The total impression received was that of extreme intellectual deterioration.

At all times when he was asked, the patient said that he was able to see. He moved about in his room as though he could see and constantly bumped into objects. When this was pointed out to him, he used excuses such as: "It is a little dark"; "This is not a bright day," and "I'm tired." When asked directly whether he was blind, he vigorously denied it, though at times he would say "I don't see as well as I did before, but I can see all right. I need new glasses." He made constant false guesses about the location of windows and doors and the appearance of persons in his environment. His memory for forms and colors was correct. The syndrome of denial of blindness remained constant as long as a psychologic examination was possible, which was approximately until the first week of June 1942.

The patient became steadily worse; both cranial flaps showed considerable ballottement, which gave his head a grotesque appearance. In May and June 1942 he had episodes of severe excitement, often yelling at the top of his voice, "Murder! Murder!" He became incontinent and progressively more stuporous. At that stage a slight hemiparesis, with increased deep tendon reflexes, was noted on the right side. During the last thirty days of his life his temperature was elevated, the pulse rapid and small and respiration stertorous. He died in deep coma on July 13, 1943.

Pathoanatomic Study (Dr. Harry Zimmermann).—"The brain was tremendously distorted, with the biparietal diameter much increased as a result of a tumor in the left parietal lobe and a cerebral hernia in the right parietal region. The left parietal bone flap was adherent to the underlying cortex. The cerebral convolutions of the remainder of the brain were greatly flattened. Gyral herniations into the dura were present over both temporal lobes. The left uncus and the adjacent occipital lobe showed evidence of molding by herniation through the tentorial incisure. There is practically no cerebellar pressure cone. Frontal section through the brain at the level of the anterior commissure disclosed a huge, fungating tumor mass in the greatly dilated inferior horn of the left lateral ventricle. This mass infiltrated most of the structures of the basal ganglia on the left side. The midline of the brain had been shifted to the right. Most of the left parietal, temporal and occipital lobes were replaced by tumor tissue. The tail of the splenium of the corpus callosum was involved by the neoplasm, which extended into the right occipital lobe. In this lobe a large operative cavity was present, the walls of which contained tumor tissue.

"There were a few small, flat, calcified plaques in the meninges of the lower thoracic portion of the cord and near the conus. There was no sign of involvement by the tumor of either the spinal meninges or the cord itself."

All the other findings were normal except for aspiration pneumonia.

Anatomic Diagnosis.—The diagnosis was glioblastoma multiforme, involving both the parieto-occipital region and the basal ganglia (left); healed scars of decompressions (right and left sides); herniation of the brain (right), and aspiration pneumonia.

COMMENT

We were able to observe 6 cases of denial of blindness over a period of eighteen months in a 600 bed hospital. This fact alone demonstrates that the syndrome is not rare, but it is easily overlooked unless the examiner is aware of its existence. One is inclined to believe the statement of the patient who says he can see without an attempt at verification. Furthermore, most examiners are reluctant to make any attempt to stress forcibly to the patient such a severe defect as blindness. All patients who present such a syndrome are deteriorated and have disturbances of retention and orientation, hallucinations and delusions, and neuropsychiatrists may look at their denial of blindness as one of many psychotic manifestations. Moreover, in most cases it is of little practical significance whether these blind patients affirm or deny their blindness, and the syndrome is therefore predominantly of theoretic interest.

The symptoms of the syndrome are fairly uniform, in contrast to the anosognosia of a hemiplegia, which may vary from mere imperception of the weakness to denial of the existence of the paralyzed extremities (Nielsen[19]). The symptoms in our cases, as well as those in all cases described in the literature, may be discussed under the following headings:

1. The patients do not perceive their blindness, act as though they could see, report visual experiences and deny their blindness when confronted with it. 2. All patients show at least a moderate amount of intellectual deterioration. 3. The patients have disturbances of orientation, defects of memory and retention and a tendency to confabulation. 4. All of our patients had an amnestic aphasia. 5. The most frequent cause for the blindness of such patients is bilateral

19. Nielsen, J. M.: Disturbances of the Body Scheme, Bull. Los Angeles Neurol. Soc. **3**:127-136, 1938.

hemianopsia due to occipital or temporoparietal lesions.

One of the most striking features in the behavior of our patients was their inability to learn from their experiences. As they were not aware of their blindness when they walked about, they bumped into the furniture and walls but did not change their behavior. When confronted with their blindness in a rather pointed fashion, they would either deny any visual difficulty or remark: "It is so dark in the room; why don't they turn the light on?"; "I forgot my glasses," or "My vision is not too good, but I can see all right." The patients would not accept any demonstration or assurance which would prove their blindness. The behavior of these persons reminds one of psychotic patients with a fixed delusional system which cannot be refuted. As they refuse to accept rather simple and convincing proofs of their blindness, one is at first inclined to regard their behavior as a mixture of malingering and hysterical reactions as they occur in the Ganser state. However, in their premorbid personality no trace of such tendencies can be found. Of course, one may satisfy oneself with the rather general explanation that their organic cerebral disease is responsible for a regression to more primitive hysterical patterns of behavior, in which the denial of their most important defect is of paramount importance.

All our patients showed considerable intellectual deterioration. This was obvious in clinical examination, in standard intelligence tests and in special examinations designed by Goldstein [20] to test abstract and concrete behavior. The deterioration alone, however, does not adequately explain the denial of blindness. It would be difficult to understand how any degree of intellectual impairment would lead to imperception of the patients' lack of vision. Their inability to learn from experience may be partly explained by their severe impairment of retention. Such a defect of retention and memory for recent events with disorientation and confabulations occurred in all our patients. E. Redlich and Bonvicini [10] noticed it in their own observations but did not stress it as a universal feature from a descriptive point of view. Anton's syndrome may be said to consist of a Korsakoff psychosis in a blind person. The existence of visual hallucinations alone in a blind person does not necessarily constitute Anton's syndrome. Such hallucinations in the blind without denial of blindness are not uncommon in persons with dementia paralytica. In all our patients an amnestic aphasia was present.

Anton's syndrome is not a constant and unchanging phenomenon. This was noted particularly by E. Redlich and Bonvicini [10] and reflects our own experience. Patients like P. K. and A. J. (cases 6 and 3), who suffered from progressive cerebral lesions, showed the syndrome constantly, while others exhibited a good deal of fluctuation in their perception of blindness, as did J. C. (case 4). In J. C. the syndrome was observed only for a few days.

The fluctuations speak somehow against the possibility of strict localization of any lesion which may be responsible for the syndrome. Such fluctuations can be demonstrated in most cortical syndromes, and they speak in favor of holistic interpretations of disturbances of higher cerebral functions, as classified by Goldstein.[21] The question of localization has been discussed by some authors. Anton [1a] did not assume any strict localization but expressed the opinion that imperception of blindness is due to rather generalized lesions in the brain, such as destruction of a major portion of the long association fibers. Thus, impairment of one sensory sphere will not be conveyed to other parts of the brain and imperception of the defect will result. Redlich and Bonvicini [10] were even more general in their statements and assumed that any diffuse cerebral impairment in a blind person may lead to the syndrome, though the majority of patients show lesions of the occipital lobe. Poetzl [12] assumed that the syndrome is due to strictly localized interruptions between thalamic and cortical centers. He claimed such localization in his cases of anosognosia and autotopagnosia, particularly hemiplegia on the left. In case studies Wortis and Dattner,[22] Gerstmann,[23] Nielsen [19] and Olsen and Ruby [24] assumed a similar point of view. Experimental work by Dusser de Barenne and McCulloch [25] and theoretic considerations by Cobb [26] point to the existence of reverberating circuits

20. Goldstein, K.: A Case of Aphasia with Special Reference to the Problems of Repetition and Word Finding, J. Neurol. & Psychiat. **1**:333-341, 1938.

21. Goldstein, K.: The Organism, New York, American Book Company, 1939.

22. Wortis, H., and Dattner, B.: An Analysis of a Somatic Delusion, Psychosom. Med. **4**:319-323, 1942.

23. Gerstmann, J.: Problem of Imperception of Disease and of Impaired Body Territories with Organic Lesions: Relations to Body Scheme and Its Disorders, Arch. Neurol. & Psychiat. **48**: 890-913 (Dec.) 1942.

24. Olsen, C. W., and Ruby, C.: Anosognosia and Autotopagnosia, Arch. Neurol. & Psychiat. **46**:340-344, (Aug.) 1941.

25. Dusser de Barenne, J. G., and McCulloch, W. S.: Direct Functional Interrelation of Sensory Cortex and Optic Thalamus, J. Neurophysiol. **1**:176-185, 1938.

26. Cobb, S.: Borderlands of Psychiatry, Cambridge, Mass., Harvard University Press, 1943.

and interaction between thalamus and sensory cortex which will bring about conscious representation and integration of the sensual spheres. This interaction between thalamus and sensory cortex seems responsible for conscious representation of the body (the body image as Schilder [27] called it) and for conscious experience of the sensual spheres. As Cobb put it, these reverberating circuits between thalamus and sensory cortex are responsible for a state of neural vigilance, awareness of self and environment. One may say that they are responsible for conscious "experiencing." Kahn's [28] thesis that "experiencing" is characteristic of the integrated human organism but is absent in animals, infants and deteriorated and disintegrated patients might find its neurologic substrate by a further study of the normal and impaired function of these reverberating circuits. Bilateral lesions between the visual thalamus and the visual cortex or lesions involving some of their connecting fibers seem to be responsible for an imperception of blindness. Whether such lesions alone will prove to be the cause of an imperception of blindness cannot be stated with certainty because all our patients, in addition to those described in the literature, have shown generalized disease of the brain as well as any such focal lesion.

The causes of blindness in patients who deny their blindness may be varied. Four patients showed bilateral hemianopsia; but 1 patient was blind as the result of secondary optic nerve atrophy, and the amaurosis of another was due to diabetic retinopathy. The cause of the blindness seems to be irrelevant in the pathogenesis of Anton's syndrome, although apparently bilateral hemianopsia is more frequent than the unilateral form. For reasons which are not understood, most persons do not notice a hemianopsia, with the exception of patients with migraine, who report an actual halving of their visual fields. Goldstein studied one aspect of this phenomenon in his treatise on pseudofovea. The last word on this imperception of hemianopsia, particularly of vision obscure and vision nulle of the old French authors, has not been said. One may assume that some patients with bilateral hemianopsia do not perceive their blindness because they do not notice the loss of any part of their vision; i. e., they do not notice their hemianopsia.

At times normal blind persons have a need to disguise their blindness and to act as though they could see. Romain Rolland described such a case in the blind girl in "Jean Christophe." It may be assumed that this tendency will occasionally play a role in cases in which a pathologic condition of the brain exists. Denial of blindness as a pure hysterical symptom has not been observed; disturbances of the body scheme in hysterical states, schizophrenia and symptomatic psychoses are well known and were described by Schilder,[27] Bychowski [29] and others. The syndrome is in some ways the opposite of so-called apperceptive blindness, in which condition the patient is able to see but behaves as though he were blind because he is unable to apperceive "visual impressions of a chaotic outer world" (Patterson and Stengel [30]). Furthermore, the degree of insight which patients with visual agnosias have may vary considerably during the course of the illness (Adler [31]). In 1 patient (J. C.), with a temporary state of deterioration, we thought that psychologic reintegration was accompanied with perception of his blindness. Imperception of blindness undoubtedly is related to the disturbances of the body scheme described as anosognosia and autotopagnosia, and to the imperception of sensory aphasia. Such disturbances may be predominantly due to focal lesions; however, we have not reachced a complete explanation from neurologic studies. In most cases a combined neurologic and psychiatric approach throws some light on such syndromes.

SUMMARY

The blindness of 6 patients presenting the syndrome of denial of their own blindness was caused by diabetic retinopathy, in 1 patient; by atrophy of the optic nerve, in another, and by bilateral hemianopsia due to tumor or to vascular lesions, in 4 patients. Moreover, all patients had diffuse cerebral lesions. All showed intellectual deterioration: disorientation, severe impairment of recent memory and retention, and confabulation. The existence of bilateral focal lesions of the visual radiations or of the occipital visual areas leading to bilateral hemianopsia seems to play an important role in the pathogenesis of the syndrome. The interruptions of reverberating circuits between the thalamus and the sensory cortex constitute the outstanding etiologic factor.

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27. Schilder, P.: The Image and Appearance of the Human Body, London, Kegan Paul, Trench, Trubner & Co., Ltd., 1935.

28. Kahn, E.: Personal communication to the authors.

29. Bychowski, G.: Disorders in the Body Image in the Clinical Pictures of Psychoses, J. Nerv. & Ment. Dis. **97**:310-335, 1943.

30. Patterson, M. T., and Stengel, E.: Apperceptive Blindness in Lissauer's Dementia Paralytica, J. Neurol. & Psychiat. **6**:83-86, 1944.

31. Adler, A.: Disintegration and Restoration of Optic Recognition in Visual Agnosia, Arch. Neurol. & Psychiat. **51**:243-259 (March) 1944.

SYNKINETIC PUPILLARY PHENOMENA AND THE ARGYLL ROBERTSON PUPIL

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From time to time the Argyll Robertson pupil has been attributed to a lesion outside the central nervous system, as in the oculomotor nerve, the ciliary ganglion or the ciliary nerves. The most recent proponents of this theory are Nathan and Turner.[1] On the basis of 2 cases of their own and of 8 cases collected from the literature, they concluded that the Argyll Robertson pupil may be caused by damage to the peripheral efferent pathway to the iris. They also argued that there must be two efferent routes for pupillary constriction. "Parasympathetic pupillo-constrictor fibers relay not only in the . . . cells of the ciliary ganglion but also in the more peripherally situated episcleral ganglia." All their evidence, however, was casuistic, and their observations were not complete.

Although they constantly dealt with the problem, they neglected to mention the common diagnostic signs of the Argyll Robertson pupil, which are miosis, pupillary inactivity to light but constriction on convergence, and poor dilator response to locally instilled mydriatics. None of their cases had all these essential features. The criteria that Nathan and Turner set for themselves were as follows:

> (*a*) The pupil on the normal side must contract when the affected side is stimulated; (*b*) the affected pupil must not contract to light or dilate in darkness either directly or consensually; (*c*) both pupils must contract normally on accommodation and convergence . . . and (*d*) the lesion should be known to be peripheral.

In offering explanations for these abnormal pupillary reactions, they indirectly considered the possibility that nerve regeneration might produce synkinesias, which, in turn, would lead to pupillary constriction on convergence but not in reaction to light. They declared that the voluntary acts of accommodation and convergence may evoke a contraction of the pupil which is much stronger than the response to light reflex and that this difference should be most apparent in patients with lesions of the oculomotor nerve. Then they argued that if the so-called Argyll Robertson pupil following trauma to the oculomotor nerve were due to nerve regeneration, patients recovering from peripheral oculomotor palsy should reveal signs of an Argyll Robertson pupil, but they stated that this does not occur. The latter statement is not entirely correct. Pupillary constriction in association with ocular movements following recovery from oculomotor ophthalmoplegia does occur, and cases have been described.[2] A careful search for pupillary synkinesias will reveal them to be present in many cases of oculomotor paralysis. It is apparent that these authors did not seriously consider the possibility that such pupillary synkinesias could account for the so-called Argyll Robertson pupil. If they had, they would have stressed the fact that various movements of the eyes did or did not produce a change in the diameter of the affected pupil. Since such observations were not mentioned in their report, it is doubted whether Nathan and Turner were dealing with the classic syndrome of the Argyll Robertson pupil.

Personal observations have disclosed that the constriction in the so-called Argyll Robertson pupil following peripheral lesions of the oculomotor nerve is present not only on convergence but on downward, upward and inward movements of the ipsilateral globe. The following clinical and experimental data are reported to show that pupillary constriction on convergence may be one of several synkinesias following lesions of the oculomotor nerve.

CLINICAL DATA

CASE 1.—L. F. L., a 20 year old radio man, second class, accidentally fell from flight to hangar deck. He sustained fractures of the skull and the right femur and was unconscious for several hours. He was given emergency treatment; when he regained conscious-

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1. Nathan, P. W., and Turner, J. W. A.: Efferent Pathway for Pupillary Contraction, Brain **65**:343-351 (Dec.) 1942.

2. Bender, M. B., and Alpert, S.: Abnormal Ocular and Pupillary Movements Following Oculomotor Paralysis, Arch. Ophth. **18**:411-414 (Sept.) 1937.

ness, complete paralysis of the right oculomotor nerve was noted. The pupil was dilated and fixed to all forms of stimuli. The eyeball was deviated externally. All external ocular muscles but the superior oblique and the lateral rectus were paralyzed. A roentgenogram of the skull revealed a stellate fracture involving the right frontal bone and the sphenoid sinus.

Ten weeks after the injury, examination revealed bilateral anosmia and, in the right eye, impaired visual acuity, optic nerve atrophy, narrowing of the palpebral fissure, due to enophthalmos, and a greatly diminished corneal reflex. The ptosis disappeared, and all the ocular movements returned and appeared to be normal in the formerly affected eye. The left pupil reacted well directly and consensually to light and contracted on convergence. The right pupil measured 5 mm. in diameter and did not react directly or consensually to light stimuli. It did not dilate in the dark. This pupil contracted to a diameter of 2 mm. when the eyeball was directed downward or toward the nose. The contraction was also present on inward and, to a lesser extent, on upward gaze. The best pupillary constriction in the right eye was found to occur on downward movement of the globe. Strong closure of the lids of this eye also produced contraction of the right pupil. The right pupil dilated with atropine.

Three months after the injury there was subjective improvement. Reexamination disclosed the same findings as on previous occasions except for apparent improvement in his visual acuity, especially at a near point. However, the patient was able to see print clearly at a near point only when his affected eye was deviated in the inward, downward, upward or convergent position. Outward deviation of this eye was without effect on vision. In summary, any contraction of the formerly ophthalmoplegic muscles produced associated improvement in vision at a near point. From this it may be concluded that the apparent improvement in visual acuity was the result of synkinetic contraction of the formerly paralyzed ciliary muscle.

This case is practically identical with the cases described by Nathan and Turner and meets all their criteria. It is an example of oculomotor ophthalmoplegia with rapid but incomplete recovery, with iridoparesis and associated synkinetic phenomena as residua. On contraction of any of the formerly paralytic extraocular muscles, especially the inferior rectus, the sphincter pupillae contracted simultaneously. If this pupil were examined only for the conventional reactions to light and on convergence, the clinical picture would simulate the Argyll Robertson pupil.

Another interesting finding in this case was the synkinetic contraction of the ciliary muscle in association with action of any of the formerly ophthalmoplegic muscles.

CASE 2.—J. T. A., a 23 year old electrician's mate, first class, was injured in a motorcycle accident. He was admitted to the hospital in an unconscious state and was treated conservatively. Two days after admission he was still comatose. Lumbar puncture at this time disclosed cloudy fluid, which contained 2,600 white blood cells, with 90 per cent polymorphonuclear leukocytes. He had all the clinical signs of complicating pyogenic meningitis. With penicillin and sulfadiazine therapy he improved, so that two days after treatment with the chemical he regained consciousness. At this time it was noted he was unable to raise either eyelid. The left eye was blind. There was paralysis of all movements in both eyes, except for abduction of the right eye. A roentgenogram of the skull disclosed a fine fracture line in the left frontal sinus.

Three weeks after the injury, slight movements of each eyeball appeared, and the ptosis lessened. This improvement progressed, so that eight weeks after the injury the ocular status was as follows: Both eyes were in a divergent position, and both superior lids were partially drooped. In the left eye there was no light perception and the optic nerve appeared atrophied. Vision in the right eye was 10/10. Except for bilateral paresis of the internal rectus muscle and convergence palsy, all ocular movements were normal. The left pupil measured 4 mm. and the right pupil 3.5 mm. These measurements were made in sunlight and were found to be the same in semidarkness. Neither pupil reacted to strong light, directly or consensually. There was no dilatation in darkness. Both pupils contracted almost to a pinpoint on downward movement or on attempted convergence and to a lesser extent on upward movement. Each pupil contracted with attempted movement of the tested eye. There was no visible retraction of the superior lids on downward gaze. Both pupils dilated maximally with atropine.

This case is another example of recovery from oculomotor ophthalmoplegia with residual paralysis to stimulation with light and synkinetic constriction of the pupils. Were it not for the pupillary contractions in association with ocular movements other than convergence, the clinical picture would strongly simulate the syndrome described by Argyll Robertson. It is interesting and significant that in this case and in the preceding case practically all of the formerly paralyzed external ocular muscles recovered. Only the sphincter pupillae remained paretic, being inactive to light but contracting in association with movements of the eyes.

Recovery from oculomotor ophthalmoplegia does not always occur in this manner. In some instances the postophthalmoplegic synkinesias are manifest not only in the pupil but in the formerly ptosed superior eyelid, so that the eyelid retracts in association with attempted downward movement of the globe.

CASE 3.—A 42 year old woman[3] was admitted to the hospital clinic with signs of paralysis of the third, fourth and fifth cranial nerves on the left side. The causative factor was syphilis. With antisyphilitic therapy she showed progressive improvement. Fourteen weeks after the onset of the palsies there were partial recovery of adduction movements of the left eye. The left pupil, which was at first fully dilated, became small. This pupil did not react directly or consensually to light but contracted on attempted convergence. However, the pupil was also observed to contract in association with attempted downward, inward and upward movement of the left globe. Another synkinetic phenomenon was found in conjunction with the movements

3. This patient was observed at the Mount Sinai Hospital, New York.

of this globe. Not only did the pupil contract, but the partially ptotic superior eyelid retracted synkinetically on attempted convergence, downward or inward movement of the left eye.

In this case of syphilis, had it not been for the synkinetic phenomena, the left pupil would have been readily classified as the Argyll Robertson type. In this case the synkinetic phenomena were apparent not only in the sphincter pupillae muscle but in the superior eyelid. The retraction of the eyelid in association with ocular movements has been called the pseudo-Graefe phenomenon.[4]

EXPERIMENTAL DATA

The so-called pseudo-Graefe phenomenon, or retraction of the superior lid in association with downward movement of the eye, is a synkinesia which is invariably found on recovery from ophthalmoplegia due to section of the intracranial portion of the oculomotor nerve in the monkey and the chimpanzee.[5] In some of these monkeys the pupil which is fixed to light contracts on convergence, adduction or downward or upward movement of the affected eye ten weeks after the ophthalmoplegia is experimentally produced. The following is a condensed protocol of observations made on a monkey.[6]

Experiment 1.—The subject of the experiment was a young male Macaca mulatta, weighing 2,800 Gm. The ocular reactions were normal.

Operation (Oct. 20, 1936).—A large bone flap, extending beyond the midline, was turned down on the left side, and, by gentle elevation of the temporal lobe, the optic and oculomotor nerves, the pituitary stalk and the cavernous sinus were brought into view. The oculomotor nerve was then cut with long-handled scissors, and the two ends were drawn apart 2 to 3 mm.

Postoperative Notes.—At the end of the operation the left pupil was dilated, and when the monkey began to recover from the anesthesia, the total oculomotor ophthalmoplegia of the left eye became apparent. The next day the left eyelid exhibited complete ptosis, with external deviation of the globe. The only movement remaining was outward deviation (external rectus muscle). The left pupil was dilated and "fixed" to all forms of stimulation with light.

Sixth Day: The ptosis began to diminish.

Twenty-Second Day: The ptosis was less apparent. The margin of the left upper eyelid was at the upper pole of the maximally dilated pupil.

Twenty-Eighth Day: When the monkey looked down with its right eye, its right eyelid descended synchronously; there was no downward movement of the left eyeball and none of the eyelid (earliest manifestation of the pseudo-Graefe sign). Downward movement of both superior eyelids was noted during spontaneous blinking and in response to visual or corneal stimulation.

Thirtieth Day: When the monkey looked down with its right eye, the left upper eyelid retracted. This was the first sign of recovery of muscular movement (a synkinetic response).

Thirty-Second Day: Slight action of the internal rectus muscle was noted in the left eye, the globe being adducted slightly beyond the midline in conjugate gaze to the right.

Thirty-Fourth Day: Ptosis had completely disappeared.

Thirty-Sixth Day: A slight decrease in pupillary diameter was observed.

Forty-First Day: Action of the internal rectus muscle had completely returned, the left eyeball moving well inward in horizontal excursions. The left pupil was still dilated to a diameter of 6 mm. and was inactive to light.

Forty-Ninth Day: When the animal looked to the right, both globes moved equally well in the horizontal plane, but the left superior eyelid retracted and the left globe moved slightly inward.

Seventy-Sixth Day: The diameter of the left pupil had been reduced to 3 mm. The only visible motion in the left eye was in the horizontal plane. The left pupil exhibited some decrease in diameter in association with fixation at a near point, but there was no response to light (sign of synkinetic constriction of the pupil).

Second Operation (seventy-seventh day, Jan. 5, 1937).—Stimulation of the cervical portion of the left sympathetic trunk with the animal under anesthesia induced with sodium amytal caused dilation of the left pupil, slight exophthalmos and some retraction of both the upper and the lower eyelid. The sympathetic trunk was then resected and the superior cervical ganglion crushed.

Postoperative Notes.—First Day: Piloparalysis on the left side of the face was conspicuous. The left pupil was 2 mm. in diameter and did not react to light. The pseudo-Graefe sign (synkinetic retraction of the lid) was still present. There was some enophthalmos, with secondary elevation of the edge of the lower lid, but no true ptosis.

Seventh Day: When the monkey looked down with the right eye, the left upper eyelid moved up, while the left globe move inward. When he looked up with his right eye, the left eyeball moved slightly inward, while the left pupil constricted to a slight degree (synkinetic phenomena). Direct and consensual response to light was still absent in the left pupil.

Thirteenth Day: When the animal looked at a point near or to the right, requiring action of the left internal rectus muscle, the left pupil contracted from 3 to 1.5 mm. in diameter (synkinetic phenomenon). There was no reaction to light.

Fortieth Day: When the lids closed, there were a slight contraction of the left pupil and more pronounced contraction of the right pupil (lid closure reflex).[6a] Bell's phenomenon was not observed.

Fifty-Fifth Day: The left pupil was 4 mm. in diameter.

Fifty-Sixth Day: The left pupil was 3.5 mm. in diameter.

4. Bender, M. B.: The Nerve Supply to the Orbicularis Muscle and the Physiology of Movements of the Upper Eyelid (with Particular Reference to the Pseudo-Graefe Phenomenon), Arch. Ophth. **15**:21-30 (Jan.) 1936.

5. Bender, M. B., and Fulton, J. F.: Factors in Functional Recovery Following Section of the Oculomotor Nerve in Monkeys, J. Neurol. & Psychiat. **2**: 285-292 (Oct.) 1939; Functional Recovery in Ocular Muscles of a Chimpanzee After Section of the Oculomotor Nerve, J. Neurophysiol. **1**:144-151 (March) 1938.

6. These experiments were performed in the laboratory of physiology, Yale University, New Haven, Conn.

6a. Bender, M. B.: Eyelid Closure Reaction; Arch. Ophth. **29**:435-440 (March) 1943.

Sixtieth Day: The left pupil was 2.5 mm. in diameter.

Sixty-First Day: The left pupil contracted from 2.5 to 1.5 mm. in association with convergence. It still did not react to light. In this respect the left pupil had the characteristics of an Argyll Robertson pupil.

Seventy-First Day: The diameter of the left pupil remained at 2.5 mm. The pupil did not dilate in the dark. When the monkey attempted to look down, up or to the right, the abnormal movements of the upper eyelid and the internal rectus muscle of the left eye were evident, and the apparent Argyll Robertson phenomenon was also manifest.

Third Operation (seventy-ninth day, March 26, 1937).—The bone flap was reelevated and the reunited left oculomotor nerve again severed.

Postoperative Notes.—First Day: Ophthalmoplegia was complete in the left eye, as after the first operation.

Third Day: Ptosis on the left side was incomplete; the pupil was 6 mm. in diameter and was fixed to all forms of stimuli, and the globe could be abducted but not adducted.

Tenth Day: The left palpebral fissure was 5 mm. wide. No change in the left pupil was evident.

Twenty-Fifth Day: The ptosis was half complete. The left pupil measured 4.5 mm. in diameter.

Thirty-Fifth Day: The left palpebral fissure was almost completely open, and the pseudo-Graefe sign was apparent. The left eyeball could be adducted slightly beyond the midline.

Thirty-Eighth Day: There was complete recovery in power of elevating the left lid and in adduction of the globe.

Forty-First Day: When the right eye looked down, the left upper eyelid moved up, and the left eyeball moved slightly inward. The left pupil measured 4 mm. in diameter.

Sixty-Third Day: When the left eye moved nasally the left pupil became smaller. The pupil also contracted slightly when the monkey fixated at a near point.

Eighty-Sixth Day: The left pupil was 3.5 mm. in diameter. It contracted slightly in association with closure of the lids.

One Hundred and Twenty-Fifth Day: The left pupil was observed under a magnifying glass and was found to contract in association with fixation at a near point, on adduction of the globe and with closure of the lids. Synkinetic phenomena were also present in the left upper lid on downward movement of the globe. The ocular status at this time revealed upward movements in the left upper eyelid which were synchronous with action of the internal rectus muscle and with vertical (up and down) or dextral movements of the normal right eye. Vertical movements in the left eye were absent.[7]

Two Hundred and Seventy-Eighth Day: The left pupil showed a definite reaction to light.

Four Hundred and Fortieth Day: The ocular status was unchanged. The left pupil failed to enlarge in low illumination.

7. Recovery of vertical movements in the affected eye was never apparent. This, however, did not mean that the elevators or depressors of the globe remained paralyzed; on the contrary, the absence of upward or downward movements was due to simultaneous contraction in the elevators and depressors of the eye, which resulted in absence of movement. When in the eye recovering from ophthalmoplegia the inferior rectus muscle had been previously cut upward movements of the globe became apparent; that is, as soon as one of the antagonists was eliminated the action of the other became apparent.

These experiments show that the syndrome simulating the Argyll Robertson pupil may be reproduced in the monkey by sectioning the oculomotor nerve intracranially and permitting regeneration to take place. The signs of regeneration are (1) recovery of adduction, (2) synkinetic retraction of the superior lid in association with attempted downward, upward or inward movement of the formerly ophthalmoplegic eye and (3) synkinetic contraction of the pupil. This pupil, which becomes progressively miotic during the period of recovery, does not react directly or consensually to light but contracts conspicuously in association with attempted vertical and inward movements of the affected globe.

That these pupillary reactions are not due to structural changes in the ciliary ganglion or the ciliary nerves is borne out by the fact that the oculomotor nerve was twice cut intracranially and that the apparent Argyll Robertson pupil became manifest each time after a definite interval in the stage of recovery from the ophthalmoplegia.

Experiment 2.—Pupilloconstrictor fibers are known to course in the ciliary nerves. The theory that another pupilloconstrictor pathway may exist in other branches of the oculomotor nerve, such as those innervating the inferior rectus and inferior oblique muscles, is refuted by the following simple experiment. Intraorbital section of the branches of the oculomotor nerve other than the ciliary nerves produced no changes in the pupil. The pupil in the monkey employed reacted well to light and on convergence. Subsequent intracranial section of the ipsilateral oculomotor nerve in the same monkey produced the pupillary effects described in experiment 1. In other words, there appears to be no basis for the claim that some of the pupilloconstrictor fibers may travel through the inferior branches of the oculomotor nerve, external to the ciliary ganglion.

Experiment 3.—Intraorbital section of the ciliary ganglion or the ciliary nerves alone or in combination with destruction of the adjacent optic nerve in the monkey or cat produced complete iridoplegia with no constriction to light or in convergence. However, eight to ten weeks after this section there were signs of nerve regeneration. The pupil began to react well both directly and consensually to light and to contract on convergence.[8] There was no difference between the reaction to light and the response on convergence. There were no signs suggestive of the Argyll Robertson pupil.

Experiment 4.—A partial lesion, such as section of the superior fibers of the oculomotor nerve trunk in its intracranial course, produced complete but transient ophthalmoplegia in the monkey. This was followed by rapid recovery in all functions of the external ocular muscles. The sphincter pupillae, however, remained paretic for a longer time. In 1 monkey with such an experimental lesion there was almost complete recovery from the ophthalmoplegia on the fifteenth postoperative day. There was no ptosis, and downward, upward and

8. In cases in which the adjacent optic nerve was crushed, the direct reaction to light remained lost while the consensual response was restored.

inward motion of the globe appeared normal. However, the pupil, which measured 6 mm. in diameter, was fixed to light. On the thirtieth postoperative day the pupil, smaller in diameter, began to react sluggishly to light both directly and consensually; the pupillary constriction on convergence seemed to be brisker than that to light. In other words, regeneration or recovery from oculomotor ophthalmoplegia appeared to be most retarded in pupillary reaction to stimulation with light. Noteworthy was the absence of ocular synkinesis in the monkey with incomplete section of the oculomotor nerve.

COMMENT

The clinical and experimental data herewith presented clearly indicate that the pupillary changes which appear after an oculomotor ophthalmoplegia are not the typical reactions found with the classic Argyll Robertson pupil. Although such a pupil is fixed to light, it reacts not only on convergence but in association with internal and vertical movements of the affected eye.

It may be asked why the postophthalmoplegic pupil reacts on convergence but not to light. This may be due to the fact that light, which is a relatively weak stimulus, does not produce a reflex motor response sufficiently strong to penetrate the functional block caused by the scar in the healing oculomotor nerve trunk.[9] On the other hand, the motor energy evoked by the act of convergence, or by a strong attempt at vertical or internal movement of the eye, is adequate for the impulse to pass through the scar to all the regenerated axon fibers. Since the newly formed axis-cylinders branch freely and grow indiscriminately into the distal stump, it is readily understood why an impulse intended for one group of muscles may be shunted at the scar via the regenerated nerve fibrils to other muscle masses.[10] Thus, an impulse to the internal, the inferior or the superior rectus muscle may cause widespread contractions so that all the muscles supplied by the formerly injured oculomotor nerve act simultaneously. Whether all muscles contract to an equal degree depends on the extent of the lesion, the number of nerve fibers regenerated, how extensively the regenerated axis-cylinders branch and how much nerve energy is discharged into the oculomotor nerve.

The pupillary constriction found in association with movements of the globe may not be of the same degree for each of the individual movements. Thus, it has been found that in some cases the pupil contracts only in association with downward gaze, or only with internal movements of the eye or on convergence. In still other cases the pupil contracts on attempted upward gaze or with movements in any direction or directions effected by the recovered ocular muscles. The type and degree of pupillary constriction vary with the mode of regeneration and with other factors previously stated. From these clinical and experimental observations, it is apparent that the so-called Argyll Robertson pupil which occurs after a lesion in the oculomotor nerve is due to partial regeneration of fibers to the sphincter pupillae muscle and synkinetic contraction of the iris in association with movements in the rest of the eyeball. Consequently, it is erroneous to classify this pupil as the one described by Argyll Robertson. If, for the sake of brevity or expressive meaning, an eponym is preferred, the term "pseudo Argyll Robertson pupil" may be employed, just as "pseudo-Graefe sign" is used to denote synkinetic retraction of the lid.

SUMMARY

After an oculomotor ophthalmoplegia the iris may be found to contract on convergence but not to light, thus simulating the Argyll Robertson pupil. Closer examination, however, discloses that this pupil reacts not only on convergence, but synkinetically with other movements, namely, downward, inward or upward movement of the affected globe. The synkinetic pupillary constriction may sometimes be associated with synkinetic retraction of the lid. The phenomena of synkinetic pupillary constriction and retraction of the eyelid can be reproduced experimentally by intracranial section of the oculomotor nerve in the monkey. These phenomena are partly explained by the theory of indiscriminate regeneration of oculomotor nerve fibers. It is concluded that the so-called, or pseudo, Argyll Robertson pupil, sometimes noted after head injury with a complicating oculomotor ophthalmoplegia, has no etiologic relationship to the classic pupillary reaction originally described by Argyll Robertson.

9. In the experimental monkey, the threshold of an electrical stimulus necessary to evoke a contraction of an ocular muscle or pupillary constriction is much higher in that part of the regenerated oculomotor nerve which runs to the scar than in the part which leaves it. Apparently, the scar partially blocks the impulses originating in the nucleus of the oculomotor nerve.

10. To account for the synkinetic contractions which follow regeneration of the oculomotor or the facial nerve, consideration must be given to the functional and anatomic changes which may accompany regeneration in the entire motor neuron unit in question. The changes may occur at the ganglion cell body, at the nerve scar or at the motor end plate and muscle. The probability is that all the points mentioned are involved, but most of the experimental evidence at hand indicates that the chief cause of the synkinetic phenomena is the indiscriminate regeneration of axis-cylinders at the scar. Bender.[5]

LATERAL SPINOTHALAMIC TRACT AND ASSOCIATED TRACTS IN MAN

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The whole problem of peripheral pain reception and central pain perception and representation remains one of the fundamental fields of investigation in neurophysiology and clinical neurology. Certain aspects of the problem are of considerable interest to the neurosurgeon. For many patients suffering from persistent intractable pain of organic origin, interruption of the central pain pathways offers a palliative measure. Because dorsal root section severs all afferent paths to the spinal cord, the most successful central interruption is obtained by cutting the lateral spinothalamic tract somewhere along its course. Its relatively superficial position renders it accessible to anterolateral chordotomy, to an incision dorsolateral to the inferior olivary nucleus or to an incision at the lateral sulcus of the mesencephalon. The literature concerning this neurosurgical field has been extensively reviewed,[1] and only pertinent references will be included here.

These neurosurgical procedures depend partly for their success on an accurate anatomic knowledge of the pathways concerned. Clinical and experimental evidence indicates that painful stimuli affect free nerve endings and that the resulting impulses travel centrally over nonmyelinated and myelinated processes of unipolar cells in cerebrospinal ganglia. The central processes of these cells enter the spinal tract of the trigeminal nerve or the dorsolateral fasciculus of the spinal cord. The central path in the spinal cord probably originates from large cells in the dorsal gray matter of the opposite side and, to some extent, of the same side[2] and ascends in the lateral funiculus as the lateral spinothalamic tract, in close association with the spinotectal and the dorsal and ventral spinocerebellar tracts. Approximately the same path is followed by impulses originating from thermal stimuli, although the initial receptors are more complex.

There are certain anatomic and physiologic points concerning this pathway which need clarification.

1. It is not certain how large the axons of the central pain path may be, or how much change occurs after the first and subsequent synapses. It has been stated that the lateral spinothalamic tract contains axons more heavily myelinated than the axons in the peripheral paths.[3] It would be of fundamental interest to know that there are actually more heavily myelinated axons centrally than peripherally. The presence of numbers of nonmyelinated axons in the lateral spinothalamic tract might well lead to false impressions of its size and location if such impressions were based entirely on the Marchi reaction.

2. Although it seems fairly well established that the decussation of fibers in this tract occurs in about one segment,[2] further studies on this point would be valuable in establishing the range of variation, particularly in upper and lower levels of the cord.

3. The degree of lamination within the tract remains to be more definitely determined. It is also thought that axons carrying impulses due to thermal stimuli ascend in the lateral spinothalamic tract, but the extent to which these axons are segregated is still uncertain.

4. Apparently not all the axons in this tract go directly to the thalamus.[4] Some impulses are said to ascend by means of a series of short

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1. (*a*) Grant, F. C.: Surgical Methods for the Relief of Pain, J. A. M. A. **116**:567-571 (Feb. 15) 1941. (*b*) Rasmussen, A. T., and Peyton, W. T.: The Location of the Lateral Spinothalamic Tract in the Brain Stem of Man, Surgery **10**:699-710 (Nov.) 1941. (*c*) Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract at the Level of the Inferior Olive, Arch. Neurol. & Psychiat. **47**:293-304 (Feb.) 1942. (*d*) Walker, A. E.: The Spinothalamic Tract in Man, ibid. **43**:284-298 (Feb.) 1940.

2. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

3. Mettler, F. A.: Neuroanatomy, St. Louis, C. V. Mosby Company, 1942.

4. May, W. P.: The Afferent Path, Brain **29**:742-803, 1906.

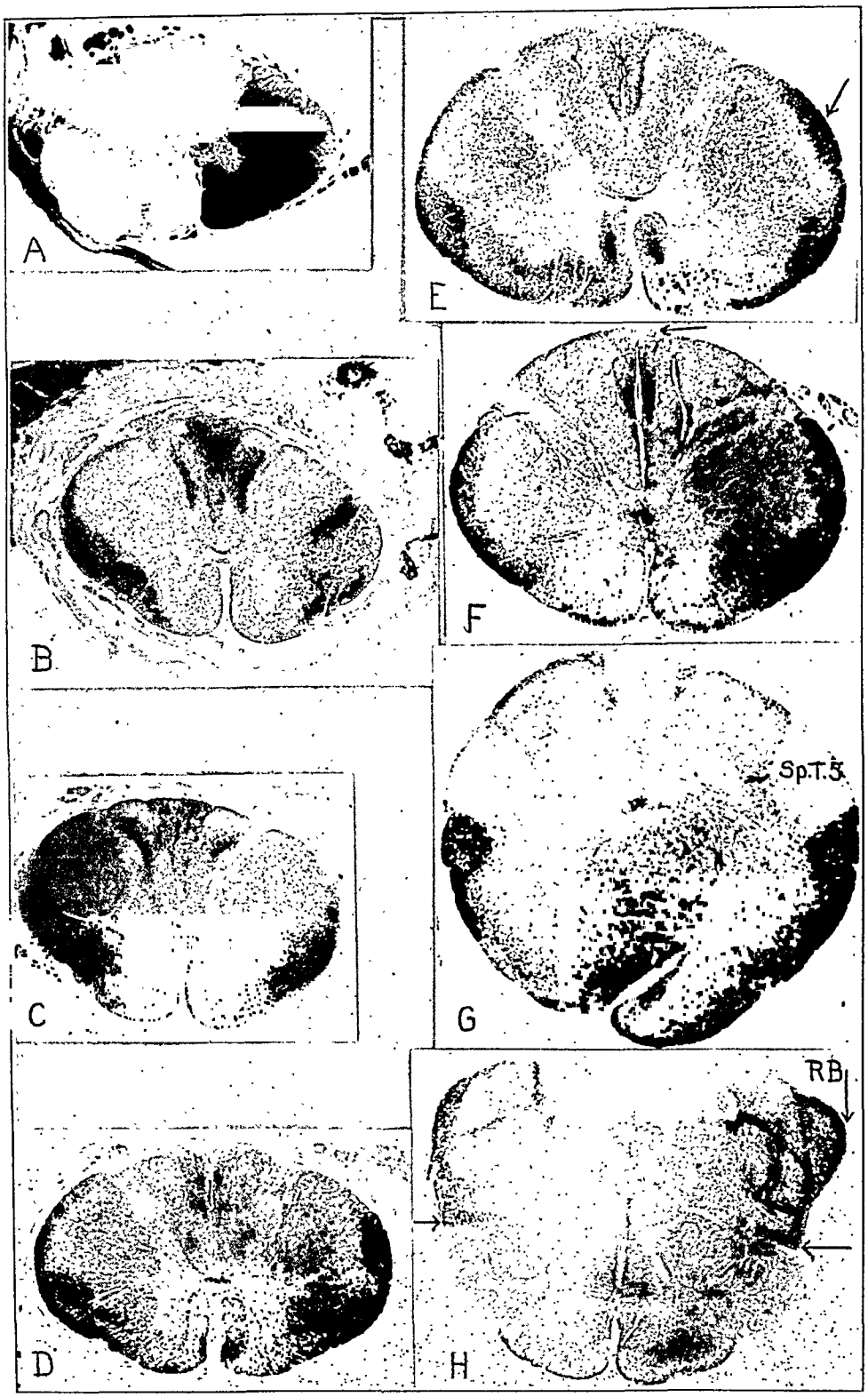

Fig. 1.—Unretouched photographs of cross sections of the spinal cord, the left side throughout corresponding to the left side of the page.

A, a section through the sixth thoracic segment. The lesion on the left side is confined to the lateral funiculus. Weigert method; × 4.5.

B, section through the fifth thoracic segment of the cord, between the two lesions. On the left side is a compact area of degenerating fibers ascending from the lower lesion. On the right side is a more scattered area of degenerating fibers descending from the upper incision. Degeneration resulting from the tabetic process is present in the posterior funiculi. Marchi method; × 4.5.

C, section from the third thoracic segment of the cord. The degeneration on both sides is confined to the lateral funiculi and includes lateral spinothalamic, spinotectal and dorsal and ventral spinocerebellar fibers. Marchi method; × 4.5.

D, section from the second thoracic segment of the cord, in which the increasing concentration on the surface and the dorsal shifting of dorsal spinocerebellar fibers are apparent. Marchi method; × 4.5.

(Legends continued on opposite page)

chains, which are probably situated in the gray matter. Previous observations indicate that after chordotomy the number of degenerating axons decreases rostrally.[1b]

5. The extent of bilateral representation is uncertain. Unilateral chordotomy fails to abolish pain completely, especially in viscera, so that when visceral pain is present bilateral chordotomy is usually necessary. Even then, according to Foerster and Gagel,[2] pain may return, and to explain this they postulated the development of accessory paths in the posterior funiculi.

Any single morphologic or physiologic method is inadequate to settle these points completely. Certain questions, however, such as the exact topography and lamination of the lateral spinothalamic tract, the amount of its ascent while decussating and the degree of intermingling with other tracts can be much more definitely settled if all available human material is adequately studied and reported. Unfortunately, for human material the Marchi stain is the best available morphologic technic. The well known faults of this technic, as well as the infrequency with which cases come to autopsy at the optimum time interval, set a limit on the usefulness of this method. As yet, too few cases have been reported to permit definite knowledge even of the normal range of variation.

MATERIALS AND METHODS

This report is based on a study of the spinal cord and brain stem of a man aged 57 who had a bilateral chordotomy for relief of pains in the legs and tabetic crises. The lesions were made in the upper thoracic portion of the cord, at the sixth thoracic segment on the left side and between the fourth and the fifth thoracic segment on the right side. After operation there was subjective relief of all pain in the legs and gastric crises. In addition, there was loss of pain and temperature sense up to the sixth thoracic dermatomal area on the left side and to the seventh thoracic dermatomal area on the right side. After operation the patient's course was progressively downhill. Pyelonephritis, cortical abscesses of both kidneys and probable uremia developed. All these complications apparently originated from chronic tabetic paresis of the bladder. The patient *died twenty-one days after the operation, an interval* with the time range of an optimum Marchi reaction in man.

The brain and spinal cord were removed about six hours after death and fixed by immersion in a 10 per cent concentration of solution of formaldehyde U. S. P. Subsequently, selected levels of the spinal cord and brain stem were cut into slices 2 to 3 mm. thick and prepared by the Swank-Davenport[5] modification of the Marchi technic. The slices were dehydrated, embedded in pyroxylin of low viscosity and cut transversely at 60 microns. In general, this method is excellent, and the background is usually free of troublesome artefacts. In this case there was some precipitation of osmic acid in normal areas, particularly in the heavily myelinated tracts of the brain stem, but the areas of true degeneration were sharply outlined and easily followed throughout the spinal cord and the brain stem.

Other slices of the brain stem were dehydrated, embedded in either paraffin or pyroxylin and, after being sectioned, stained with iron hematoxylin, cresyl violet, the activated silver albumose method of Bodian or the Mallory-azocarmine method.

The smallest sections were photographed directly. The largest sections were projected on to drawing material at a magnification of six to eight and the sections outlined. The degeneration was indicated by stippling, the process being checked by microscopic examination. In addition, the areas which were stippled in were photographed directly at higher magnifications.

RESULTS

In this case the chordotomy on each side was performed by inserting the knife at the denticulate ligament to a depth of 4 mm. and bringing it out at the line of exit of the ventral root fibers. Weigert stains of sections from the operative levels indicated that the incisions were confined to the lateral funiculi (fig. 1 *A*). Marchi stains of sections between the two incisions contained descending degeneration on the right side, while ascending degenerating fibers from the lower incision could be clearly seen in the lateral funiculus on the left side (fig. 1 *B*). The descending degeneration lessened as the fibers shifted medially toward the gray matter in lower segments, indicating that the degeneration was due mainly to the interruption of bulbospinal fibers. No major involvement of the pyramidal tracts was apparent on either

5. Swank, R. L., and Davenport, H. A.: Chlorate-Osmic-Formalin Method for Staining Degenerating Myelin, *Stain Technol.* **10**:87-90 (July) 1935.

E, section from the fifth cervical segment. The degeneration in the lateral funiculi occupies a surface position, and the dorsal spinocerebellar tract (indicated by the arrow) is clearly evident. Marchi method; × 4.5.

F, section from the second cervical segment. The degenerating fibers extend between the dorsal and the ventral roots on the surface. The tendency of degeneration in the posterior funiculi to ascend in the fasciculus gracilis is indicated by the arrow. Marchi method; × 4.5.

G, section at the level of the pyramidal decussation. The compact areas of degeneration immediately ventral to the spinal tract and nucleus of the trigeminal nerve, *Sp. Tr. 5*, on each side are sharply delineated. Marchi method; × 4.5.

H, section through the inferior olivary nuclei. The dorsal spinocerebellar fibers are entering the restiform bodies, *R B*. This section corresponds to the drawing in figure 3 *A*, and the positions of the lateral spinothalamic tracts are indicated by the arrows. Marchi method; × 3.

side. In a section immediately above the incision on the right side (fig. 1 *C*) the degeneration occupied an area corresponding but roughly to the area interrupted by the knife, but still confined to the lateral funiculus. Differentiation here between the lateral spinothalamic and other tracts was not possible. In sections through higher levels of the spinal cord, shifting of the involved fibers toward the periphery was practically identical on the two sides, except that the degeneration resulting from the more rostrally placed incision on the right side was somewhat heavier (fig. 1 *D* to *F*). In addition to this clearly indicated lamination, there was a tendency at cervical levels to a shifting dorsally of what were apparently dorsal spinocerebellar fibers (fig. 1 *E* and *F*). On entering the medulla the fibers became concentrated, and in a section through the decussation of the pyramids the degeneration was crowded into a relatively small area immediately ventral to the spinal tract and nucleus of the trigeminal nerve on each side (fig. 1 *G*). These tracts were actually more compact here than at any other part of their course through the brain stem.

Degenerating fibers were present in the posterior funiculi throughout the cord (fig. 1 *B* to *F*), and these were a result of the tabetic process. The complete destruction of other fibers due to the chronic process is illustrated in the sections stained by the Weigert method shown in figure 2, *A* and *B*. This degeneration could be traced into the medulla, particularly to the nuclei of the fasciculi graciles, but was not apparent in the medial lemnisci.

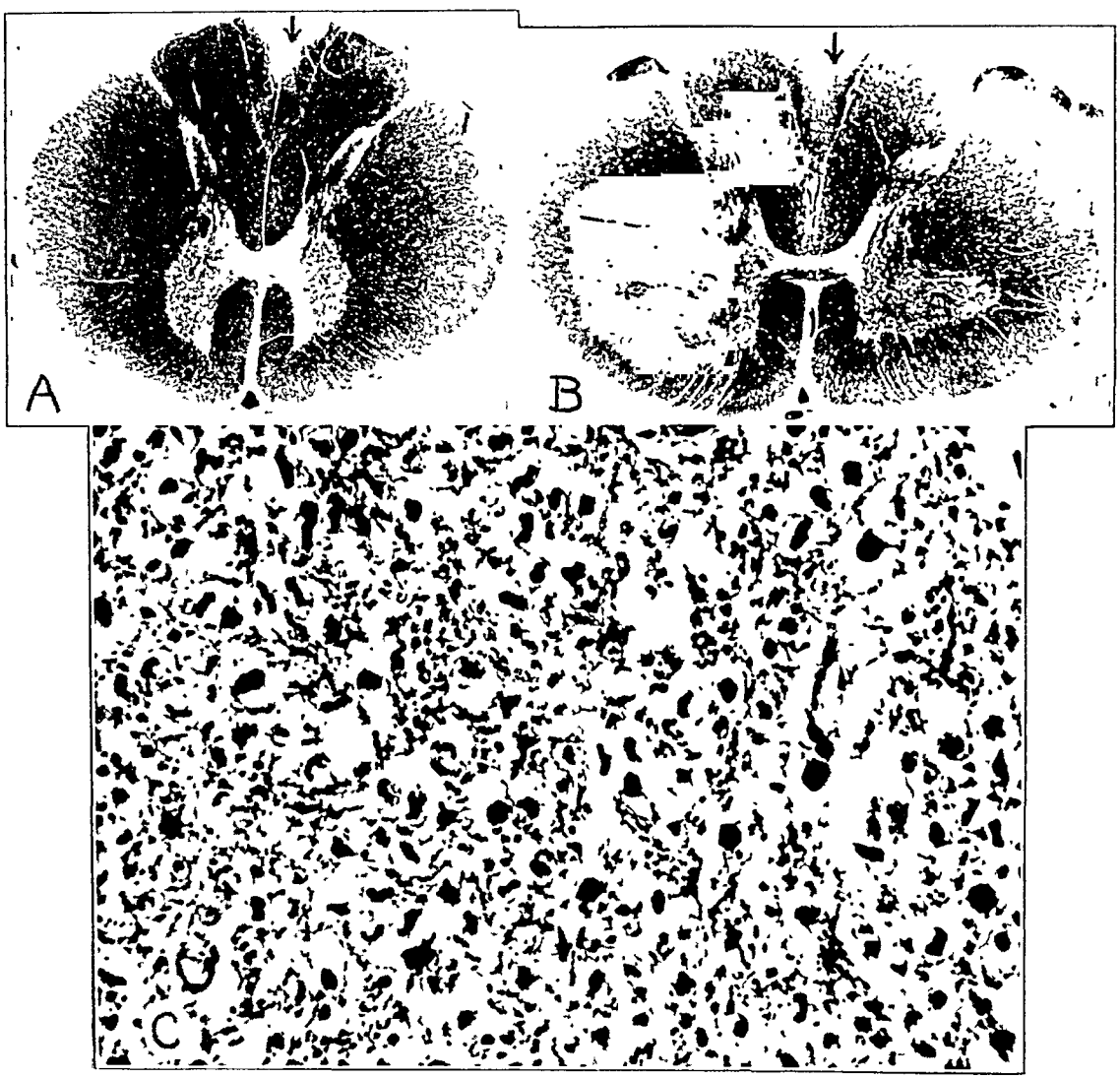

Fig. 2.—*A*, cross section through the first cervical segment, illustrating the degeneration in the fasciculi graciles (arrow). Weigert method; × 6.

B, cross section through the fifth cervical segment of the cord, illustrating peripheral degeneration in the lateral funiculi, as well as degeneration in the fasciculi graciles (arrow). Weigert method; × 6.

C, photomicrograph of the area occupied by the lateral spinothalamic tract. This section is from the second thoracic segment and therefore contains normal fibers. It illustrates the relatively large numbers of nonmyelinated and small myelinated axons in this area. It is not possible to say, however, that these axons actually belong to the lateral spinothalamic tract. Bodian's activated silver albumose method; × 400.

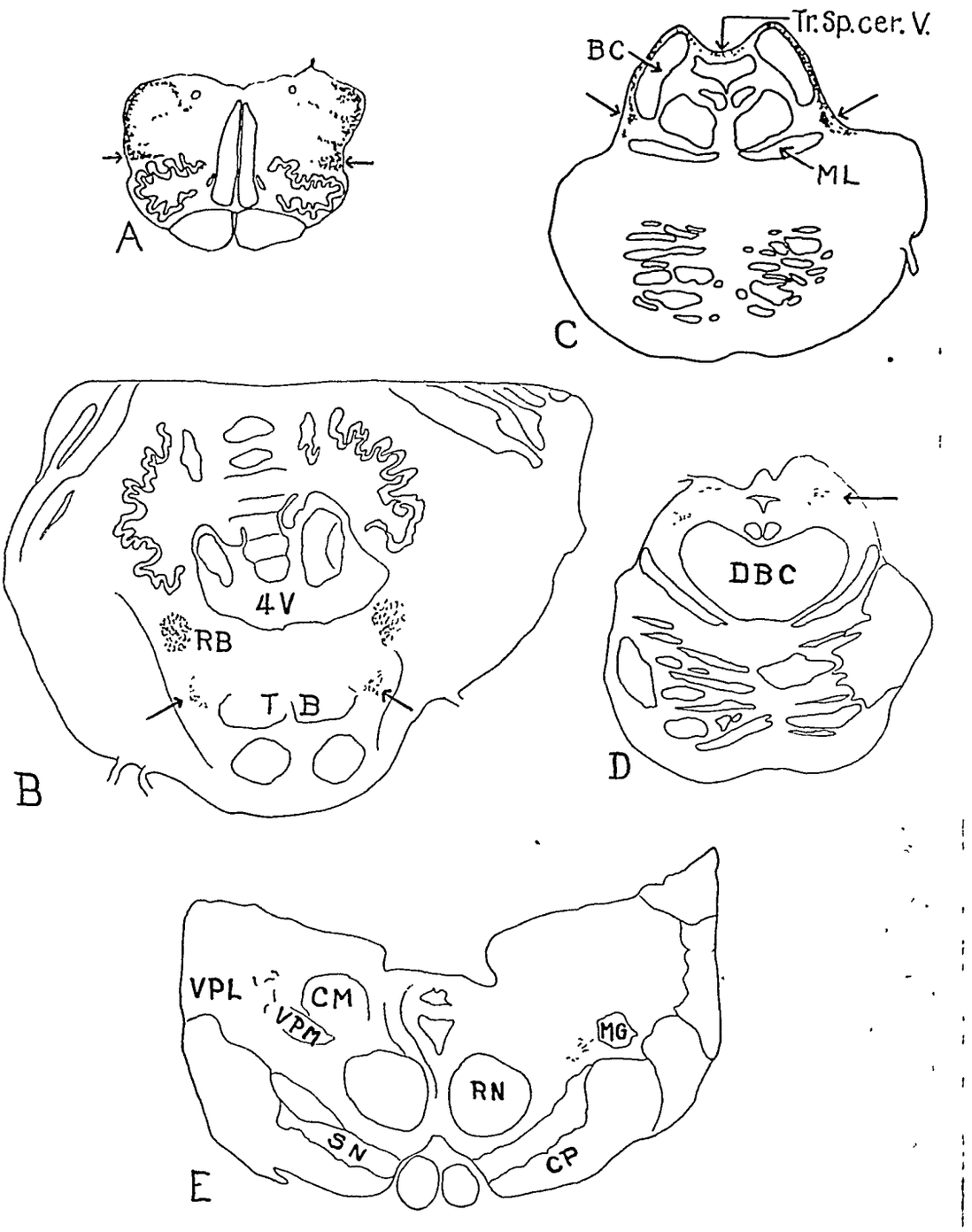

Fig. 3.—Drawings illustrating the course and relative density of degenerating fibers as they ascend in the brain stem; × 1.5 diameters. The specific areas, in addition, are represented in the photomicrographs of figure 4.

A, drawing of a section through the inferior olivary nuclei, illustrating the positions of the lateral spinothalamic tracts (arrows) dorsolateral to the inferior olives. The dorsal spinocerebellar fibers are shifting dorsally into the restiform bodies, and the intermediate positions are occupied mainly by ventral spinocerebellar fibers. This section was also photographed directly (fig. 1 *H*).

B, drawing of a section through the lower part of the pons, indicating the positions of the lateral spinothalamic, spinotectal and ventral spinocerebellar fibers (arrows) dorsolateral to the trapezoid bodies, *T B*. The restiform bodies, containing degenerating dorsal spinocerebellar fibers, lie still more dorsally. *4 V* is the fourth ventricle See figure 4 *A* for photomicrograph of the degenerating fibers.

C, drawing of a section through the upper part of the pons, showing the spinotectal and lateral spinothalamic tracts (arrows) dorsal to the medial lemnisci, *M L*. The ventral spinocerebellar tracts, *Tr. Sp. cer. V.*, are shown entering the anterior medullary velum after shifting dorsally across the brachia conjunctiva, *B C*. See figure 4 *B* for a photomicrograph of the degeneration.

D, drawing of a section through the inferior colliculi, showing the incorporation of the lateral spinothalamic tract into the triangular area at the base of the inferior colliculus (arrow) and the entrance of spinotectal fibers into the inferior colliculus. For a photomicrograph of this area see figure 4 *C*. Decussation of brachia conjunctiva, *D B C*.

E, drawing of a section through the inferior portion of the nucleus ventralis posterolateralis (*V P L*) of the thalamus, indicating the scattered degeneration on each side. This is indicated also in figure 4 *D*. *R N* indicates the red nucleus; *C M*, the centromedian nucleus; *V P M*, the nucleus ventralis posteromedialis; *M G*, the medial geniculate body; *C P*, cerebral peduncles; *S N*, the substantia nigra.

In ascending through the medulla the dorsal spinocerebellar fibers on each side shifted dorsally across the spinal tract of the trigeminal nerve and entered the restiform body (figs. 1 *H* and 3 *A*). This relatively heavy degeneration continued to indicate sharply the restiform bodies as they entered the cerebellum.

Rostral to the formation of the restiform bodies the degeneration was composed of ventral spinocerebellar, spinotectal and lateral spinothalamic fibers, with the ventral spinocerebellar fibers the most superficial. All the fibers occupied a medullary position identical with that described by Schwartz and O'Leary [1c] in that they were dorsolateral to the inferior olivary nucleus and extended medially for a distance indicated in figure 3 *A*. This conforms with the observation of these authors that fibers from lower segments occupy a more lateral position in the medulla. The position described was maintained until the pons was reached. In the lower part of the pons the degeneration was just lateral and slightly dorsal to the trapezoid body (fig. 3 *B*), and of course was much less superficially placed than in the medulla. Because of the increase in pontile fibers and nuclei in the upper part of the pons, there occurred a relative shift dorsally in the position of the degenerating fibers, and also of the lateral and

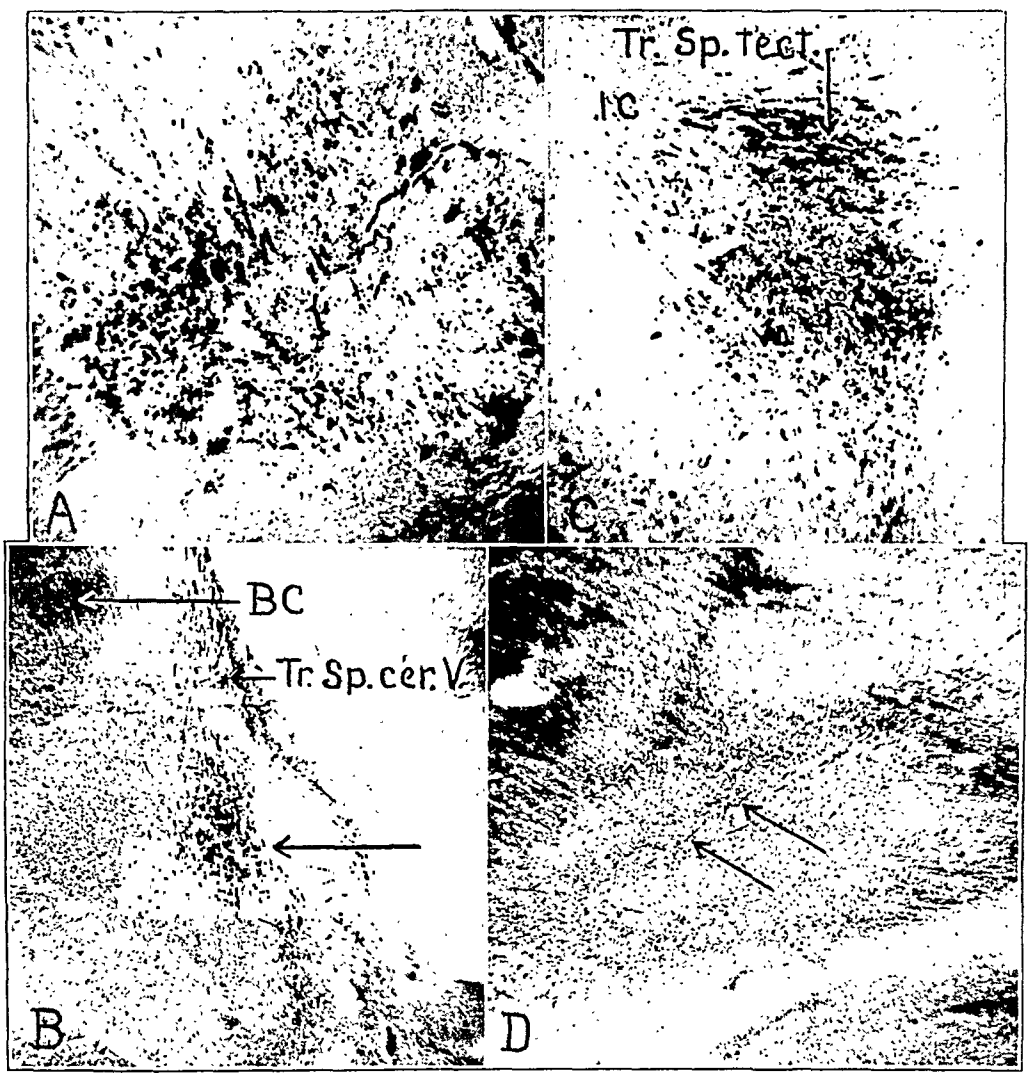

Fig. 4.—Photomicrographs of the areas of degeneration indicated by stippling in figure 3, *B* to *E*. × 20 diameters.

(*A*) The area contains degenerating fibers of the lateral spinothalamic, spinotectal and ventral spinocerebellar tracts (see figure 3 *B*).

(*B*) At this level the lateral spinothalamic and spinotectal fibers (arrow) become incorporated into the base of the lateral lemniscus along the lateral sulcus. Ventral spinocerebellar fibers, *Tr. Sp. cer. V.*, can be seen shifting dorsally across the brachium conjunctivum, *B C*. See figure 3 *C*.

(*C*) Lateral spinothalamic fibers lie at the base of the inferior colliculus (arrow). Spinotectal fibers, *Tr. Sp. tect.*, can be distinguished, since they are oriented transversely as they enter the inferior colliculus, *I C*. See figure 3 *D*.

(*D*) The few degenerating fibers present as the lateral spinothalamic tract enters the thalamus are partially indicated by arrows. See figure 3 *E*.

medial lemnisci. At the level of the anterior medullary velum the degenerating fibers were clearly associated with the lateral lemnisci. Also, at this level ventral spinocerebellar fibers turned dorsally across the surface of the brachium conjunctivum on each side into the anterior medullary velum (figs. 3 *C* and 4 *B*). Rostral to this, only spinotectal and lateral spinothalamic fibers remained. At the level of the inferior colliculi, spinotectal fibers entered the inferior colliculus (figs. 3 *D* and 4 *C*), while the lateral spinothalamic fibers passed through the heavily myelinated triangular area at the base of the colliculus. These fibers ascended in relatively the same position, medial, first to the inferior quadrigeminate brachium and then to the medial geniculate body (fig. 3 *E*) and entered the nucleus ventralis posterolateralis of the thalamus. Fewer degenerating fibers were noted here than at lower levels, but there was no doubt that they ended in this part of the thalamus. Sections above this level revealed no degeneration.

COMMENT

Comparison of the results of the postoperative sensory examinations with the operative levels reveals that after the fibers of the pain pathway enter the cord they cross completely within at least two segments. The incision on the left side of the sixth thoracic segment, for instance, spared fibers derived from the seventh thoracic dermatomal area but included the fibers from the eighth. This, however, gives no indication of the amount of ascent after the first synapse.

The course of the lateral spinothalamic tract as traced with the Marchi technic agrees fairly well with that described by previous observers.[1] The results in this case show that the lateral spinothalamic tract is most easily attacked surgically at its relatively superficial position in the thoracic portion of the cord,[1a] in the medulla[1c] and along the lateral sulcus of the mesencephalon.[6] They also indicate that the usual anterolateral chordotomy interrupts relatively few descending fibers. Some of the degeneration noted below the incisions may have been retrograde, but most of it probably represented degenerating bulbospinal fibers. Anterolateral chordotomy also interrupts part of the dorsal spinocerebellar fibers and probably all of the ventral spinocerebellar fibers, as well as the spinotectal and lateral spinothalamic fibers. The relatively heavy involvement of the dorsal spinocerebellar tract in this case is somewhat surprising. From the extent of the incisions one would expect most of these fibers to be spared. Either the tract extends farther ventrally than is commonly supposed,[2] or postoperative edema in the neighborhood of the incisions affected many of the fibers.

The degeneration throughout the cord was confined to the superficial portions of the lateral funiculi. The incisions did not extend into the anterior funiculi; and since relief was obtained, it is most probable that the lateral spinothalamic fibers ascend only in the lateral funiculi. Hyndman and Van Epps[7] suggested that some of the pain fibers ascend in the anterior funiculi and that because of this incisions must extend into this area, or even to the ventral median fissure. However, their evidence for this assumption is by no means conclusive. They presented Marchi preparations of the spinal cord only in the neighborhood of the incisions, and these showed precipitation of osmic acid in apparently normal areas, which rendered detailed interpretation valueless. Degeneration was present in the anterior funiculi, but this is to be expected, since with these areas cut the ventral spinothalamic tracts will degenerate. The weight of evidence is against a spread as far anterior as this. It must be said, however, that too few detailed examinations and reports are available in the literature to enable one to be dogmatic on this point.

In the cervical portion of the cord the degenerating fibers were more concentrated on the surface and were more dorsally situated, indicating the development of lamination by the entrance and crossing of fibers derived from the cervical and upper thoracic levels. From a comparison of this case with other cases, it is apparent, as other investigators have decided, that there is considerable intermingling of fibers from different levels,[8] so that there is by no means a sharp segmental demarcation within the tract. Because of this it is somewhat difficult to accept the degree of exact topical localization which Hyndman and Van Epps postulated. They stated in their conclusions that with a selected incision analgesia could be confined to the chest. In their one illustrative case, however, analgesia was present over the abdomen, as well as the chest, and initially over the upper portions of the thighs as well.

6. (*a*) Walker, A. E.: Relief of Pain by Mesencephalic Tractotomy, Arch. Neurol. & Psychiat. **48**: 865-880 (Dec.) 1942. (*b*) Dogliotti, A. M.: First Surgical Sections, in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145 (May-June) 1938.

7. Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract, Arch. Surg. **38**:1036-1053 (June) 1939.

8. Stookey, B.: The Management of Intractable Pain by Chordotomy, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:416-433, 1943.

This observation was, rather, in agreement with the amount of lamination that actually exists in the cord.

The relative lamination present in the medulla is confirmed by comparison of this case and the case of Rasmussen and Peyton [1b] with that of Schwartz and O'Leary.[1c] The last-mentioned authors reported on the total degeneration resulting from an intramedullary tractotomy and by the depths of their incisions showed that fibers from the lower dermatomal areas were more superficially placed. The observations in the present case are in accord with such a conclusion. Also confirming the observations of Dogliotti,[6b] Rasmussen and Peyton.[1b] Schwartz and O'Leary [1c] and Walker [9] is the evidence that in the upper portion of the pons and the lower part of the mesencephalon degeneration is intermingled with fibers of the lateral lemniscus. This and the course of the lateral spinothalamic tract near the base of the inferior colliculus have not yet been adequately described in the current textbooks. There is little evidence that this tract is ever incorporated in the medial lemniscus.

The relative scarcity of degenerating fibers near the thalamus is also confirmed and remains a puzzling feature. In this case, the degenerating fibers arose from the sacral, lumbar and lower thoracic levels and were therefore fewer than would be present after an intramedullary tractotomy. Nevertheless, at their entrance into the thalamus the fibers were few indeed as compared with the numbers seen at lower levels, even when the accompanying tracts are considered. Several explanations may be offered. First, the myelinated fibers composing the lateral spinothalamic tract may be fewer than is to be expected, in which case the bulk of the degeneration seen at lower levels would be due to the involvement of other tracts. If this is the case there is at present no satisfactory method of determining the nonmyelinated component of this tract (fig. 2 *C*). Or the explanation might lie in the transmission by a series of short chains, as postulated by May.[4] Lastly, it is quite possible that near the thalamus many of the fibers lose their myelin and therefore would not exhibit the Marchi reaction. These points should all be considered, but as yet not enough cases have been studied to indicate a definite answer. The number of fibers is enough, however, to establish definitely that they end in the posteroventral part of the thalamus.

9. Walker, A. E.: Somatotopic Localization of Spinothalamic and Secondary Trigeminal Tracts in Mesencephalon, Arch. Neurol. & Psychiat. **48**:884-889 (Dec.) 1942.

SUMMARY

The spinal cord and brain stem of a tabetic patient who died twenty-one days after a bilateral chordotomy were studied with the Marchi technic. The chordotomies were performed at the sixth thoracic segment on the left side and between the fourth and the fifth thoracic segment on the right side. Subjective relief of pains in the legs and gastric crises was obtained, and there was loss of pain and temperature sense up to the sixth thoracic dermatomal area on the left side and to the seventh thoracic dermatome on the right side.

Decussation of the tracts was observed to be completed within two segments, and the degeneration, as shown by the Swank-Davenport modification of the Marchi technic, was almost bilaterally symmetric in ascent. The degeneration included lateral spinothalamic, spinotectal and dorsal and ventral spinocerebellar fibers. Relative lamination was confirmed by the increasingly superficial course of the fibers in the cervical part of the cord and the lower portion of the medulla and their position dorsolateral to the inferior olivary nucleus. Incorporation of the lateral spinothalamic tract into the lateral lemniscus and the area at the base of the inferior colliculus, its entrance into the nucleus ventralis posterolateralis of the thalamus and the relative scarcity of degenerating fibers here were also established.

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ELECTROENCEPHALOGRAPHIC FINDINGS IN CASES OF BROMIDE INTOXICATION

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In 1936 and 1937 Lennox, Gibbs and Gibbs [1] first reported on the effect of bromides and barbiturates on the electroencephalograms of normal persons and of epileptic patients. In normal subjects, the intravenous administration of 5 to 10 grains (0.325 to 0.65 Gm.) of phenobarbital or 30 grains (2 Gm.) of sodium bromide produced no appreciable effect until drowsiness or sleep occurred, at which point the record resembled that obtained during natural drowsiness or sleep. In epileptic patients, on the other hand, a similar dose of either drug tended to shorten and distort the seizure discharges and to prolong the interval between discharges.

Since this early report, a number of investigators have focused their attention on the effect of drugs on the electroencephalogram, emphasis being given to the clinical phenomena accompanying the various phases of intoxication [2] and to the problem of the delirium itself.

In 1938 Rubin and Cohen [3] reported 1 case of bromide intoxication in which a mildly slow pattern (8.3 cycles per second) appeared at a blood bromide level of 59.6 mg. per hundred cubic centimeters, with an appreciable rise in frequency as the level fell to 36.7 mg. per hundred cubic centimeters. None of the slow rhythms characteristic of sleep appeared.

Recently Romano and Engel [4] have studied cases of delirium due to heterogenous disorders, such as cardiac decompensation, malignant hypertension, diabetic acidosis and Brill's disease, and have shown that slow activity is the predominant quality of the electroencephalogram during any of these delirious states, with changes toward normal paralleling clinical improvement. An interesting point was the virtual absence of fast rhythms except those of low voltage, commonly lumped together as "low voltage fast." None of their cases involved delirium due to the bromides.

Progressive slowing of the brain waves has been noted during acute induced alcoholic intoxication,[5] and a mean change in frequency of 2 to 3 cycles per second usually accompanies gross intoxication.[6] In a previous communication, Greenblatt, Levin and di Cori [7] reported a higher incidence of abnormal electroencephalograms for

Miss Marie M. Healey and Miss Helen E. Brennan gave technical assistance.

From the Department of Psychiatry of the Harvard Medical School, and the Boston Psychopathic Hospital.

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6. Engel, G. L., and Rosenbaum, M.: Delirium: III. Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, Arch. Neurol. & Psychiat. **53**:44-50 (Jan.) 1945.

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patients suffering from alcoholic psychoses, particularly those characterized by hallucinosis or confusion, than for normal controls or for persons with chronic alcoholism without psychotic manifestations.

The presence of confusion, disorientation and memory impairment (the "organic reaction pattern"), especially in its acute form,[8] greatly increases the probability of finding dysrhythmia in any given case. In our experience the dysrhythmia is often, but not always, of the slow wave type.[9]

The present study deals with the electroencephalograms and the clinical and laboratory findings in a series of cases of bromide intoxication.

Normal and Abnormal Electroencephalograms Encountered at Various Blood Bromide Levels for Patients with Bromidism *

	Under 100 Mg./100 Cc.							100-200 Mg./100 Cc.							Over 200 Mg./100 Cc.						
	Normal Electroencephalogram	Abnormal Electroencephalogram						Normal Electroencephalogram	Abnormal Electroencephalogram						Normal Electroencephalogram	Abnormal Electroencephalogram					
Diagnosis		Fast	Slow and Fast	Slow	Total No. Abnormal	Percentage Abnormal	Total		Fast	Slow and Fast	Slow	Total No. Abnormal	Percentage Abnormal	Total		Fast	Slow and Fast	Slow	Total No. Abnormal	Percentage Abnormal	Total
Bromide psychosis	5	0	0	0	0	0	5	1	1	1	1	3	75	4	2	1	4	6	11	85	13
Bromidism with personality disorders	8	2	1	0	3	27	11	0	0	0	2	2	100	2	0	3	0	1	4	100	4
Totals	13	2	1	0	3	19	16	1	1	1	3	5	83	6	2	4	4	7	15	88	17

* Abnormal electroencephalograms are divided into those with fast, mixed slow and fast and slow activity.

METHODS

Electroencephalographic studies were made with the aid of a Grass six channel, ink-writing oscillograph. Both monopolar and bipolar tracings were taken, and whenever possible a two to three minute record of forced hyperventilation was obtained. Frontal, parietal and occipital leads were applied to both hemispheres, and interconnected leads from the mastoids or the ear lobes served as grounds. Note was made of the patient's condition at the time of the electroencephalographic study, and special attention was paid to the mental picture. Bromide blood levels for these patients were determined by the method of Wuth,[10] usually on the day of the electroencephalographic study, but a few blood bromide values had to be interpolated.

Classification of Electroencephalograms.—The tracings were classified as normal, borderline or abnormal after thorough review of the essential characteristics of each tracing and correction for the age of the patient.[11] In addition, the predominant frequency was determined and classified as follows:

Normal: 8.5 to 12 per second frequency
Fast activity: Predominant frequency above 12 cycles per second
Slow activity: Predominant frequency below 8.5 cycles per second
Mixed fast and slow: A pattern consisting of frequencies both faster and slower than the normal range

The data are both cross sectional and longitudinal. For some patients only one electroencephalogram was taken, and for others several electroencephalograms were obtained over a period. Thus, we observed not only the changes in a single patient during the course of recovery, but the differences between several patients at the same blood bromide level.

PATIENTS

A total of 39 patients referred to the Boston Psychopathic Hospital because of neuropsychiatric disturbances associated with bromide intoxication were studied. Patients with idiopathic epilepsy or known cerebral damage were eliminated from the series.

DATA AND RESULTS

Concerning the relationship between the electroencephalogram and the blood bromide level, the table shows data for the 39 patients with bromide intoxication, divided into two groups: (1) patients (22) with a disorder diagnosed as bromide psychosis; (2) patients (17) having a pronounced personality disorder with bromidism as a secondary feature. For the latter group, of 17 patients, the primary diagnoses were as follows: psychoneurosis, 3 patients; manic-depressive psychosis, 2 patients; dementia precox, 3 patients, and chronic alcoholism, 4 patients.

8. Greenblatt, M.; Levin, S., and Atwell, C.: Comparative Evaluation of Electroencephalogram and Psychological Tests of Abstraction in the Diagnosis of Brain Damage, to be published.

9. Greenblatt, M., and Levin, S.: Factors Affecting the Electroencephalogram of Patients with Neurosyphilis, Am. J. Psychiat., to be published.

10. Wuth, O.: Rational Bromide Treatment, J. A. M. A. 88:2013-2017 (June 25) 1927.

11. Greenblatt, M.: The E. E. G. in Late Post-Traumatic Cases, Am. J. Psychiat. **100**:378-386 (Nov.) 1943; Age and Electroencephalographic Abnormality in Neuropsychiatric Patients, ibid. **101**:82-90 (July) 1944.

Percentage of Abnormal Electroencephalograms and Blood Bromide Level.—For the two groups taken together, the percentage of abnormal electroencephalograms increased with the blood bromide level (fig. 1), from 19 per cent, for patients with bromide levels under 100 mg. per hundred cubic centimeters, to 88 per cent, for patients with bromide levels above 200 mg. per hundred cubic centimeters. In the two subgroups the trends are essentially similar. This is entirely in agreement with the clinical observation that the central nervous effects become more marked as the blood bromide level rises. However, it should be pointed out that patients with the same blood bromide level may have entirely different electroencephalograms.

Type of Electroencephalogram and Blood Bromide Level.—In addition to the increased percentage of abnormal electroencephalograms

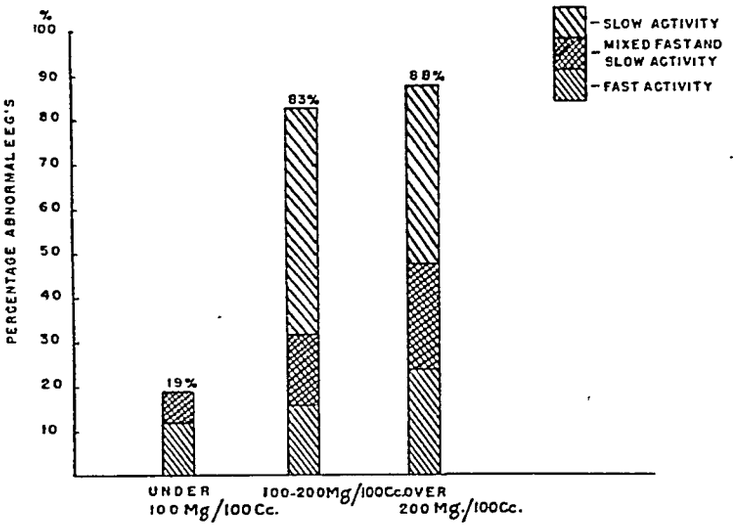

Fig. 1.—Relationship between blood bromide level and percentage of abnormal electroencephalograms. The relative number of electroencephalograms with slow, fast and mixed activity at the various blood bromide levels is also indicated. Read as follows: With 100 mg. of bromide per hundred cubic centimeters of blood, 19 per cent of patients had abnormal electroencephalograms, of which roughly two thirds had fast activity and one third mixed fast and slow activity.

with increased blood bromide levels, there appeared to be, in a number of our cases, a rather characteristic electroencephalographic trend as the blood bromide level rose, or, more strictly (since we studied patients who came to the hospital with high blood levels), as the blood bromide level fell. At high blood bromide levels the electroencephalograms of these patients showed mainly slow activity, the abnormality being diffuse. Irregular, high voltage slow waves in the 2 to 5 per second range were present in the records of 2 patients; the remainder showed frequencies mainly in the 5 to 8 per second range, with occasional slower cycles. In the intermediary ranges of blood bromide concentrations the electroencephalogram tended to show potentials faster than normal, mixed with the slow component, while at low levels of blood bromide the abnormal electroencephalograms usually exhibited abnormally fast activity. When fast activity was present, it was of 12 to 25 per second frequency as a rule and was either intermittent or continuous.

For patients with diffusely slow activity, the average bromide level was 266 mg. per hundred cubic centimeters; for patients with mixed slow and fast activity, 181 mg.; for patients with fast activity, 159 mg., and for patients with normal electroencephalograms, 90 mg., per hundred cubic centimeters.

Two noteworthy exceptions to the general trend of electroencephalographic changes were found. For 1 patient the sequence of events was rather unusual, as shown in the following tabulation:

Time After Entry	Electroencephalographic Type	Bromide Level, Mg./%	Clinical Picture
2 days	Normal 11/sec. activity	239	Confusion; hallucinosis; thick speech
12 days	Normal 11-12/sec. activity	131	Mentally clear; speech normal
24 days	Low voltage 11-14/sec. activity	39	Mentally clear; speech normal
32 days	Medium voltage 11-14/sec. activity with bursts of 18-25/sec. activity	0	Mentally clear; speech normal

This patient had severe chronic alcoholism and had indulged in bromides for one month. Although at the highest blood bromide levels his sensorium was definitely clouded, the electroencephalogram was essentially normal (11 per second rhythm). As the blood bromide level dropped, the electroencephalogram changed only slightly, the principal effect being the introduction of low and medium voltage fast waves in the 11 to 14 per second range. It would seem that the effect of bromide intoxication in this case was to slow a basically fast record to the normal range.

The same phenomenon was noted by Engel and Rosenbaum [6] in cases of acute alcoholic intoxication. When the preintoxication record showed fast or fast normal rhythms, the record during gross intoxication had a frequency distribution within the normal range. In some cases abnormally fast activity became more "normal" during intoxication.

Our other patient, who also had chronic alcoholism, had a normal electroencephalogram at an initial blood bromide level of 360 mg. per

hundred cubic centimeters. On admission this patient presented a picture similar to delirium tremens. A normal electroencephalogram in the presence of severe confusion is unusual.[12] The remarkable resistance to change in the electroencephalogram demonstrated by these 2 patients is an excellent illustration of the extremes of individual variation in response to elevations of the blood bromide.

Relation of Electroencephalogram to Clinical Symptoms.—There was a rather characteristic relationship between the electroencephalographic pattern and the clinical symptoms (fig 2). In general, a clinical picture dominated by confusion and thick speech was associated with an abnormally slow rhythm in the electroencephalogram; improvement in mental clarity and orientation was associated with mixed fast and slow activity, and the later phases of recovery were associated with either mildly fast or normal activity.

Confusion: A total of 17 out of 39 patients were confused, and the majority of these were also hallucinated. Three patients were hallucinated without confusion. (These were the only 3 patients with a diagnosis of dementia precox.) For the patients with confusion and hallucinations, the average blood bromide level was 275 mg. per hundred cubic centimeters; for those with confusion without hallucinations, the average blood bromide level was 224 mg. per hundred cubic centimeters. For 19 patients with clear mentality, the average blood bromide level was 88 mg. per hundred cubic centimeters. The electroencephalographic abnormality for patients with confusion was 88 per cent, as compared with 36 per cent for those without; and the incidence of slow activity was 60 per cent for the patients with confusion, as compared with 12.5 per cent for those without (fig. 2).

Speech Disturbance: Seventeen of the patients displayed evidence of speech disturbance, described variously as "thick speech," "dysarthria" or "slurred speech." Of these, 88 per cent had abnormal electroencephalograms, primarily showing slow activity; and the average blood bromide level for the 17 patients was 245 mg. per hundred cubic centimeters. On the other hand, of the 22 patients with normal speech, only 36 per cent had abnormal electroencephalograms; and the average blood bromide level was 92 mg. per hundred cubic centimeters. The majority of the abnormal records for patients with bromidism but with clear speech exhibited fast activity, and none of the records showed the slow type (fig. 2). All of the patients whose electroencephalograms showed abnormally slow rhythms had some speech disturbance.

Total Protein Content of Cerebrospinal Fluid: Nine patients had examination of the spinal fluid during the period of bromide intoxication. In 5 of these the total protein was elevated (over 45 mg. per hundred cubic centimeters), and in 4 it was within normal limits. No other abnormalities of the cerebrospinal fluid were found except an increased bromide content, which, unfortunately, was inadequately studied. The highest reading for total protein was 108 mg. per hundred cubic centimeters; the lowest was 25 mg. There was a rough correlation of the elevation of total protein in the cerebrospinal fluid, the electroencephalographic abnormality and the

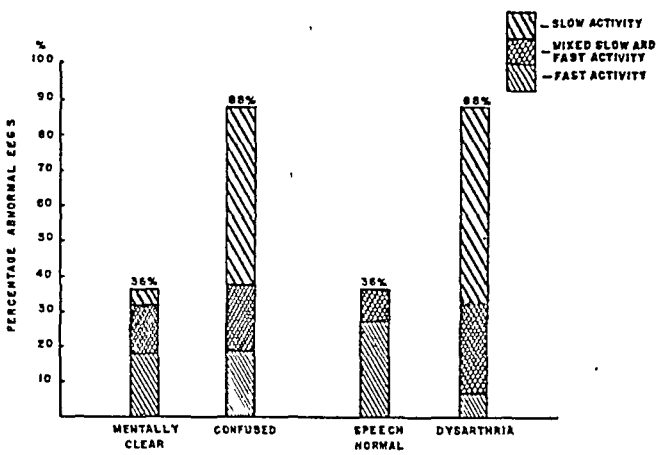

Fig. 2.—Relationship between percentage of abnormal electroencephalograms and clinical symptoms in patients with bromidism. Read as follows: Thirty-six per cent of patients with clear mentality had abnormal electroencephalograms, as compared with 88 per cent of patients with confusion. Approximately one eighth of the mentally clear patients with abnormal electroencephalograms had slow activity, whereas approximately six tenths of confused patients with abnormal electroencephalograms had slow activity.

height of the blood bromide. In 3 cases, spinal punctures were repeated during the course of recovery from bromide intoxication, and in each instance there was a significant drop in the total protein level of the cerebrospinal fluid along with a fall in the blood bromide.

Bromide Rash: Eleven of the patients had bromide rash on entry, whereas 28 were without rash on entry or at any time during the course of recovery. Blood bromide levels varied remarkably both for patients with rash and for those without; readings as high as 380 mg. of bromide per hundred cubic centimeters of blood were

12. Romano and Engel.[4] Greenblatt and others.[7] Greenblatt and Levin.[9]

obtained for persons who were entirely without cutaneous manifestations. The average blood bromide level on admission was essentially no higher for persons with eruption than for those without—229 mg., as compared with 222 mg., per hundred cubic centimeters. Electroencephalographic abnormalities were only slightly more common for persons with rash than for those without (64 per cent, as compared with 57 per cent). The data suggest that the rash is not correlated with either the blood bromide level or the electroencephalogram.

COMMENT

Three important results appear from this investigation of bromide intoxication.

1. There is a clear general trend toward increasing abnormality of the electroencephalogram with rise in the blood bromide level and progressive clouding of the patient's sensorium.

2. There is a definite tendency for the electroencephalograms of the various patients to go through similar phases of recovery—from diffusely slow activity, at high levels of bromide concentration in the blood; through mixed slow and fast activity at intermediate ranges of concentration; to fast activity, at lower ranges of concentration, and, finally, to normal activity, when the bromide is largely or entirely eliminated and the patient returns to normal both physically and mentally. The occurrence of fast activity at intermediary blood bromide levels is similar to the observation of fast activity with moderate intravenous doses of barbiturates, reported by Brazier and Finesinger.[2f] On the other hand, with delirious states not associated with drug factors, Romano and Engel[4] found that fast activity is virtually absent at all stages of the delirious process.

3. There may be remarkable individual variations in the relationship between blood bromide level and electroencephalographic abnormality. Evidently, very high blood bromide levels may at times exist even in the absence of gross electroencephalographic abnormalities. Persons may also differ considerably in the blood bromide level at which the sensorial clearing occurs. Whether the mental picture or the electroencephalogram clears first would seem to be an entirely individual matter; either is possible.

Apart from a fundamental difference in vulnerability of the nerve cell to a toxin such as bromide, other factors may be considered in attempting to account for the striking individual differences in the electroencephalographic findings at the same blood bromide levels:

(*a*) Some patients who have been indulging in bromides for a prolonged period may develop resistance to the drug, or, on the other hand, they may become more sensitive to it.

(*b*) The concentration of bromides in the extracellular fluid bathing the nerve cells may exhibit rapid or marked fluctuations (perhaps associated with the patient's hydration).

(*c*) Individual differences may exist in the effect of bromide on the permeability of the hematoencephalitic barrier. (Not only did an increased protein concentration in the cerebrospinal fluid occur concomitantly with elevation of the blood bromide level, but at the same blood bromide level there was considerable individual variation in the protein level of the cerebrospinal fluid).

Of conceivable clinical significance is the fact that all patients for whom more than one record was taken showed definite changes in the electroencephalographic pattern with time. An abnormal electroencephalogram which exhibits changes toward normal on repetition suggests the possibility of acute organic changes, such as might occur with drug intoxication. It should be borne in mind that both bromide and barbiturate intoxication may be a factor contributing to the high percentage of abnormal electroencephalograms reported in some groups of acutely psychotic patients.

SUMMARY

A study of the electroencephalograms of patients with bromide intoxication reveals the following characteristics:

The incidence of electroencephalographic abnormality is high during the intoxicated state.

A progressive clearing of the patient's sensorium parallels electroencephalographic changes toward normal.

There exists a definite relationship of the blood bromide level, the electroencephalogram and the clinical picture. At high blood bromide levels (over 200 mg. per hundred cubic centimeters) the electroencephalogram tends to show diffuse slow activity, and the patient as a rule is confused and dysarthric. Thus far, no diffusely slow activity has been found in the absence of dysarthria. As the bromide level falls, the electroencephalograms of a number of patients show a phase of mixed slow and fast activity, and

at low levels of bromide concentration the electroencephalogram shows essentially normal or mildly fast rhythms.

The electroencephalogram shows changes over a remarkable range in both frequency and voltage. High voltage activity as slow as 2 cycles per second is occasionally encountered in some of the confused patients with high blood bromide levels. Activity in the 5 to 8 cycles per second slow range is most frequent, however. On the fast side of the frequency spectrum, the activity is of medium or low voltage and is generally in the range of 12 to 25 cycles per second.

A striking phenomenon is the pronounced individual differences in the electroencephalogram and the clinical picture at the same blood bromide level.

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Case Reports

PROGRESSIVE HEMIATROPHY OF THE FACE

MAJOR HAROLD E. SIMON AND LIEUTENANT BERNARD KAYE, MEDICAL CORPS, ARMY OF THE UNITED STATES

Progressive idiopathic hemiatrophy of the face was first described by Romberg in 1846. Since then over 500 cases have been reported, including those analyzed by Archambault and Fromm [1] in 1932, when they reviewed about 400 cases in the literature and reported 3 of their own.

In the case reported by us contralateral hemihypertrophy was present. We are aware of only 1 similar reported case; this was Sterling's, cited by Archambault and Fromm.

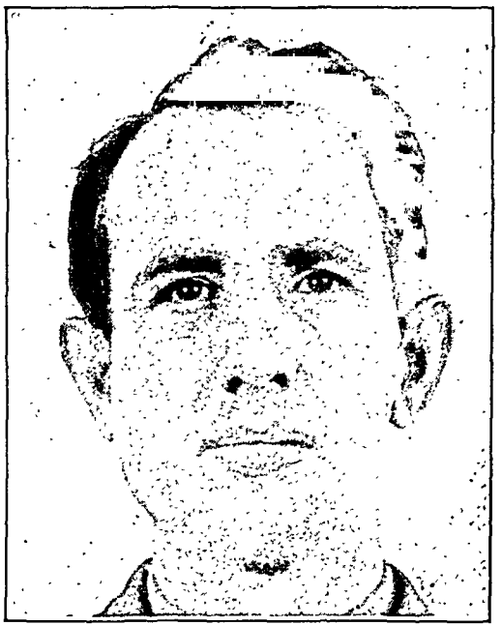
REPORT OF A CASE

The patient is a white soldier aged 28 years. His father and mother both died of cancer of the intestinal tract. He had mumps, chickenpox and diphtheria in childhood and measles in 1934. Both shoulders were dislocated and frequent minor injuries of the face were sustained while he was playing football, in 1934-1935. An infection occurred in the left external auditory canal in 1933 and in the upper lip in 1938. He received an honorable discharge from the United States Coast Guard in 1940 because of persistent seasickness, with severe emaciation and weakness, but he recovered completely after his return to civilian life.

Facial asymmetry was first called to his attention in 1938 by friends, and it was then noticed that the condition was apparent in photographs taken about eight years earlier. Just prior to the discovery of the facial atrophy there was aching of the left lower first molar tooth, which was relieved when a cavity was filled. The wasting of the left side of the face progressed until 1943, with resulting loss of strength in the muscles of mastication on that side and limitation of mastication to the right side of the face for the past five years. In recent months a throbbing sensation has been present on the affected side, and for a year frequent cramplike pains, induced by prolonged mastication or by biting on hard objects, have been noted in the right cheek. Occasionally this pain has been accompanied with momentary locking of the jaw, usually when in semiextension. Localized anesthesia, anhidrosis or alopecia has not developed.

The atrophy of the face has not progressed for a year and other areas have not become involved, but moderate progressive enlargement of the opposite side of the face has occurred. Typical migraine headaches, nervousness and increased irritability have been present since 1940. Occasionally fibrillary twitchings and transitory areas of numbness have been present in the legs.

Physical Examination.—The patient was well nourished and well developed. Asymmetry of the face was pronounced (figure): The muscles and subcutaneous tissues of the left side of the face and jaw showed extensive atrophy, involving especially the masseter and, to a lesser extent, the temporal muscle, and a muscle mass was not palpable between the mucous membrane and the skin of the left cheek. The nasolabial fold was less well defined on the left side than on the right. The facial movements were normal, but there existed definite muscular weakness, as shown by inability to hold objects firmly between the upper and lower teeth on the left side. The skin was soft and appeared normal. Pain, tactile and temperature sensations were normal and equal on the two sides of the face, and the cutaneous temperatures of the right and left cheeks were equal. Definite hypertrophy of the opposite side of the face, due largely to increased volume of the masseter muscle, was present. The results of the examination were otherwise normal. Complete ophthalmologic examination revealed nothing abnormal. The left nostril was smaller than the right, but, except for slight deviation of the septum, the intranasal structures were normal. The left ear was larger than the right. The tympanic membranes were normal, and hearing was 20/20 bilaterally. The mouth, pharynx and neck appeared normal. The patellar reflexes were notably decreased; other reflexes were normal. A small area of decreased sensitivity to pain was present in the mesial aspect of the right groin.



Appearance of patient, with atrophy of the left side and hypertrophy of the right side of the face.

Roentgenograms of the skull showed no intracranial abnormality or changes in bone. A periapical abscess of the left lower first molar tooth was apparent. The basal metabolic rate was normal. The Kahn reaction was negative; urinalysis gave normal results, and the dextrose tolerance test was within normal limits. Blood chemistry determinations showed 56 mg. of nonprotein nitrogen, 36.2 mg. of urea nitrogen, 1.6 mg. of creatinine, 208.1 mg. of cholesterol and 11.0 mg. of calcium per hundred cubic centimeters. The erythrocyte, leukocyte and differential counts were normal.

Other than extraction of the abscessed tooth, no treatment was instituted.

1. Archambault, L., and Fromm, N. K.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. **27**:529-584 (March) 1932.

CLINICAL PICTURE

Facial hemiatrophy has its greatest incidence in the second decade of life, but persons of all ages are susceptible. The onset is insidious, with gradual unilateral loss of substance of the face, usually without subjective symptoms. Typically, the atrophy is limited to one side and may involve any or all of the tissues, including the skin, subcutaneous fat, muscle, bone and cartilage. Involvement of the skin ranges from atrophy to scleroderma-like changes, and anomalies of pigmentation or variations in amount of hair on the involved side may occur. Atrophy of muscle tissue, especially of the masseter and temporal muscles, is present in most cases. Occasionally there is hemiatrophy of the tongue and, in some instances, of the palate. Atrophy of bone is apt to occur only if the onset of the disease occurs at the ages when development of bone is incomplete. Ocular and periocular changes are common and may be evidenced by ptosis, pupillary inequality, narrowing of the palpebral fissure or enophthalmos.

In many of the reported cases involvement of other portions of the body has been present, but the symptoms have presented such a wide variation that it is difficult to reconcile them with a concept of progressive facial hemiatrophy as a distinct clinical entity. It is felt, however, that some of these patients have had typical facial hemiatrophy in the presence of other, unrelated, pathologic conditions, while in others the atrophy of the face has been merely an incident in an entirely different clinical syndrome. There are no laboratory findings of significance.

Little is known concerning the pathologic changes associated with progressive facial hemiatrophy. Archambault and Fromm were able to find only 3 cases in which necropsy was performed; in 2 cases there was proliferative interstitial neuritis in all branches of the trigeminal nerve and in the gasserian and the neighboring ganglia. In the third case no neurologic lesions were found.

The etiologic factors likewise remain obscure. Lesions of the sympathetic nervous system, involvement of the trigeminal nerve or of the diencephalon, polyneuritis, chronic polioencephalitis of unknown origin and endocrine disorders have all been suggested. These theories all lack confirmation and fail to account for the various manifestations presented.

The condition usually becomes static in from one to twelve years, and in uncomplicated cases there is no tendency to serious complications or fatal termination. The value of all suggested treatments is extremely doubtful.

SUMMARY AND COMMENT

The case of progressive facial hemiatrophy associated with contralateral hemihypertrophy presented here is typical in its limitation of atrophy to one side of the face, in contrast to many of the cases reported in the literature in which atrophy of other parts of the body or other abnormalities coexisted. The associated hypertrophy of the opposite side of the face is a condition found in only 1 of the cases encountered in the literature. It may be physiologic, compensating for the weakness of the involved side and made possible by the strict unilaterality of the process and the otherwise normal, active condition of the patient.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Psychiatry and Psychopathology

PSYCHOMOTILITY IN BEHAVIOUR DISORDERS AS SEEN IN THE HANDWRITING OF CHILDREN. SELNA SCHRYVER, J. Nerv. & Ment. Dis. **100**:64 (July) 1944.

The study of a subject's handwriting gives a clue to his psychomotility, and through this, information as to his personality makeup can be obtained. With children the study of handwriting is handicapped by the subject's difficulty in spelling and by lack of routine. To overcome this the author has worked out a test in which children are asked to write a number of simple basic parts of the usual letters at least twenty times each. In a series of 100 specimens of handwriting written by a group of children with various psychiatric disorders there were indications of the intelligence level, character traits and emotional maturity of the writer. Aggressive, noisy children produced samples marked by great pressure and angularity, while preoccupied children with feelings of inferiority had small letters characterized by short endings, low pressure and hesitating beginnings. Psychotic children showed splitting of forms, exaggeration of size and contraction and alteration of forms. In evaluation of the samples, the gestalt, as well as other details, must be considered for a rounded picture.

CHODOFF, Langley Field, Va.

Meninges and Blood Vessels

MENINGOCOCCIC INFECTIONS: REPORT OF 43 CASES OF MENINGOCOCCIC MENINGITIS AND 8 CASES OF MENINGOCOCCEMIA. H. WEBSTER SMITH, LEWIS THOMAS, JOHN H. DINGLE and MAXWELL FINLAND, Ann. Int. Med. **20**:12 (Jan.) 1944.

Smith, Thomas, Dingle and Finland report on 51 patients with meningococcic infections admitted to the Boston City Hospital in the two year period beginning Sept. 1, 1940. Included among the 51 patients were 43 with meningitis and 8 with meningococcemia without clinical evidence of meningitis. The study was made in order to emphasize some of the less commonly recognized features of the clinical course, the laboratory findings and the therapy of meningococcic infections.

The authors noted from their case studies that one or more of the commoner findings of meningococcic meningitis may be absent in a given case. It was possible to make a tentative diagnosis of meningococcic meningitis in almost every instance by examination of a smear of the cerebrospinal fluid or its sediment stained with Gram's method. However, the group II meningococcus should be carefully distinguished from the gonococcus, especially in cases in which the organism is recovered only from the blood.

The initial dose of a sulfonamide drug should be administered intravenously to patients with meningitis even if they appear only moderately ill when first seen. All but 2 of the patients with meningitis who recovered showed objective signs of clinical improvement twenty-four hours or less after sulfonamide therapy.

The authors state that patients with a relative bradycardia, even though they may appear only moderately ill, should be observed for evidence of increased intracranial pressure. Lumbar puncture is of diagnostic value and should be employed as a therapeutic measure for the symptomatic relief of increased intracranial pressure. The presence of a normal sugar content of the cerebrospinal fluid following sulfonamide therapy or parenteral administration of dextrose was found to be, in itself, of no value in estimating the patient's clinical status. Pulmonary involvement was frequent in the patients with meningococcic meningitis and probably represented a local infection with the meningococcus, either alone or in association with other organisms.

There were 9 deaths among the 43 patients with meningococcic meningitis, but there were no fatalities among the 8 patients with meningococcemia.

GUTTMAN, Philadelphia.

SOME CLINICAL ASPECTS OF MENINGOCOCCIC INFECTION. F. DENNETTE ADAMS, Ann. Int. Med. **20**:33 (Jan.) 1944.

Adams discusses some of the less known or more frequently forgotten manifestations of meningococcic infection. Meningococcemia with acute meningitis, acute fulminating meningococcic septicemia (Waterhouse-Friderichsen syndrome), meningococcemia with arthritis and chronic meningococcemia are briefly considered. Meningitis may occur in any case which belongs in one of the last three groups, but the diagnosis must and can be made in the absence of symptoms and signs of meningeal involvement.

The author states that the response to sulfonamide drugs is little short of miraculous. Sulfadiazine at present is regarded as the drug of choice, with sulfathiazole a close second. He stresses the value of prompt and adequate sulfonamide therapy, the first dose being given intravenously. The condition of the patient is deemed the best guide to subsequent sulfonamide therapy. An adequate fluid intake is essential. Adams advises the use of meningococcus antitoxin for all patients who appear to be severely ill. Also, adrenal cortex extract and blood plasma may tide the patient over a period of so-called circulatory collapse.

GUTTMAN, Philadelphia.

THE MECHANISM AND TREATMENT OF RAYNAUD'S DISEASE. ISIDOR MUFSON, Ann. Int. Med. **20**:228 (Feb.) 1944.

Mufson reports 6 cases of Raynaud's disease. His observations led him to state that there exists a causal relationship between the chief somatic complaint and both the personality derangement and the emotional disturbance. Cooling of the skin is the trigger mechanism which renders complete the partial occlusion of the minute vessels, which has been initiated and is sustained by personality and social-economic derangements. It is further postulated that this cyclic type of vasospasm induces a nonspecific endarteritis, with secondary spasm and endovascular thrombi. Repeated insults of this type lead to chronic tissue hypoxia.

Mufson concludes that only a combination of therapeutic measures directed, first, toward improvement in mental hygiene and alleviation of social-economic derangements, and, second, to an increase in collateral circulation will obtain a total cure of all degrees of severity of Raynaud's disease.

GUTTMAN, Philadelphia.

TEMPORAL ARTERITIS: A LOCAL MANIFESTATION OF A SYSTEMIC DISEASE. JULIUS CHASNOFF and JEFFERSON J. VORZIMER, Ann. Int. Med. **20**:327 (Feb.) 1944.

Chasnoff and Vorzimer report the case of a patient who had arteritis of the temporal vessels. Necropsy revealed evidence of a generalized systemic arterial disease. The authors conclude that arteritis of the temporal vessels is a common local manifestation of a systemic arterial disease which must no longer be regarded as benign.

GUTTMAN, Philadelphia.

RECURRENT PNEUMOCOCCIC MENINGITIS TREATED WITH SULFONAMIDES. HENRY HOPKINS, L. C. HATCH, H. P. SCHENCK and D. S. PEPPER, Ann. Int. Med. **20**:333 (Feb.) 1944.

The authors report a case in which meningitis developed during the course of a sinusitis which was subsequently treated surgically. Type XVIII pneumococcus was isolated. The meningitis apparently subsided after administration of sulfapyridine and antipneumococcic serum. The patient experienced two more episodes of meningitis. Over a period of about thirteen weeks, 182 Gm. of sulfapyridine, 180 Gm. of sulfathiazole and 1,600,000 units of antipneumococcic serum were administered. Recovery was apparently complete.

GUTTMAN, Philadelphia.

BIOLOGIC FALSE POSITIVE SPINAL FLUID WASSERMANN REACTIONS ASSOCIATED WITH MENINGITIS. VIRGIL SCOTT, FRANK W. REYNOLDS and CHARLES F. MOHR, Am. J. Syph., Gonor. & Ven. Dis. **28**:431 (July) 1944.

Scott, Reynolds and Mohr report 7 cases of confirmed false positive reactions of the spinal fluid of nonsyphilitic persons during the course of meningitis. In 3 cases the meningitis was of tuberculous, in 2 of meningococcic, and in 2 of aseptic lymphocytic type. An additional case is included in which transfer of reagin from the blood to the spinal fluid may have occurred during an illness characterized by aseptic lymphocytic meningitis. These cases were from a series of 271 cases of meningitis of one of the types mentioned.

Unconfirmed positive Wassermann reactions of the spinal fluid were observed in an additional 20 cases of various types of acute intracranial disease occurring in nonsyphilitic patients. These cases were from a series of 200 cases of such diseases as pneumococcic, influenzal, streptococcic and staphylococcic meningitis; poliomyelitis; subarachnoid hemorrhage, and tumor of the cerebellopontile angle. The authors state that the positive Wassermann reactions could have been due to a technical error.

These observations indicate that in view of the occurrence of false positive Wassermann reactions of the spinal fluid, the diagnosis of neurosyphilis, based solely on the Wassermann reaction, is unjustified in cases of meningitis and other types of acute intracranial processes until repeated tests performed after the condition has completely subsided demonstrate the continued presence of reagin. False reactions are usually short lived, for in 7 of the 8 cases reported in this series the reaction was transitory.

GUTTMAN, Philadelphia.

Diseases of the Brain

THE CLINICAL ASPECTS OF TRAUMATIC EPILEPSY. D. DENNY-BROWN, Am. J. Psychiat. **100**:585 (March) 1944.

Denny-Brown, in reviewing the status of traumatic epilepsy, states that for this purpose head injury should be defined as injury to the skull which might directly or indirectly cause damage to the brain. Gunshot wounds resulting in penetration of the dura are twice as likely to produce epilepsy as are those which penetrate only the scalp and bone. Scalp wounds due to missiles produce epilepsy more readily than similar wounds caused by blunt instruments. The high liability to epilepsy is therefore inherent in localized injury to the brain; this is in contrast to concussion, which is a generalized cerebral disturbance. The incidence of traumatic epilepsy is much lower in civilian than in military practice. While some confusion exists in the literature regarding the importance of foreign bodies within the cerebrum, it appears that in themselves they do not materially increase the tendency to seizures. Wound sepsis, however, operates strongly in favor of the development of seizures. The duration of post-traumatic amnesia is an indication only of generalized cerebral disturbance and is not related to the development of seizures. The average time interval between the head injury and the first seizure is over two years, with extremes as great as twenty years. Denny-Brown states there is a common association of quasifugue states and traumatic epilepsy. A personality change, usually not clearcut, toward impulsive, irritable, reckless behavior may herald the appearance of epilepsy. Minor attacks, commonly preceded by a vertiginous aura, may be a precursor of traumatic epilepsy. Denny-Brown believes that neither the immediate nor the later electroencephalographic changes associated with head injury and seizures can be related to the presence of hereditary epilepsy. He indicates that not all epileptogenic scars are cerebrodural and that some are not fibrous. Jacksonian attacks or seizures with focal onset occur in less than one-half the cases of traumatic epilepsy, and localized jacksonian epilepsy has an excellent prognosis for surgical treatment.

FORSTER, Philadelphia.

THE ELECTROENCEPHALOGRAM IN POST-TRAUMATIC EPILEPSY. FREDERIC A. GIBBS, WALTER R. WEGNER and E. L. GIBBS, Am. J. Psychiat. **100**:738 (May) 1944.

Gibbs, Wegner and Gibbs point out that the amount of abnormality present in the electroencephalogram after head injury depends on the physical force applied to the brain, the ability of the brain to withstand the blow and the time that has elapsed after the injury. They divided their material into cases of mild and cases of severe head injury and studied it in relation to the importance of age and the time interval after injury. They studied 175 cases of post-traumatic epilepsy and 215 cases of head injury without convulsions. The latter group was further divided into cases of mild and cases of severe head injury. In all cases electro-

encephalograms were taken three or more months after the injury, so that only the chronic post-traumatic state was considered. The records of the three groups of post-traumatic patients were compared with the records of 1,161 epileptic patients and of 1,000 normal control subjects.

In patients with severe head injuries but without seizures the incidence of abnormalities in the electro-encephalograms continued to decrease from three months to two years after injury, while within the same time limits there was a slight decrease in abnormalities in the records of patients with post-traumatic epilepsy. Mild head injuries were found to increase but slightly the incidence of abnormalities over that found for the control group, whereas with severe head injuries the incidence of abnormalities was more than twice that for the control group. After head injury, children were more likely than adults to have abnormalities in the electroencephalogram, and they showed a greater tendency to focal abnormalities. Focal abnormalities of the electroencephalogram were four times as common for patients with post-traumatic epilepsy as they were for unselected epileptic patients. Their appearance correlated well with the occurrence of focal seizures and strongly suggested focal damage to the brain.

The incidence of focal disturbances of the electroencephalogram for patients with post-traumatic epilepsy was twenty-one times that for patients with head injury without seizures.

Gibbs, Wegner and Gibbs state that subjective complaints after head injury cannot be correlated with electroencephalographic abnormalities and that a normal electroencephalogram does not exclude the possibility of cerebral damage or post-traumatic epilepsy. They give a detailed statistical evaluation of the presence of normal and abnormal patients, both focal and generalized, in the electroencephalogram after head injury.

FORSTER, Philadelphia.

ENCEPHALOPATHY, NEPHROSIS, AND RENAL GRANULOMA FOLLOWING SULFONAMIDE THERAPY. BERNARD MAISEL, CHARLES S. KUBIK and JAMES B. AYER, Ann. Int. Med. **20**:311 (Feb.) 1944.

Maisel, Kubik and Ayer report a case in which the outstanding symptom was somnolence to the point of stupor. The patient was very sensitive to mushrooms, and on several occasions mushoom soup was followed by nausea and loss of consciousness. The current disturbance in the state of consciousness followed a twenty-four day period of oral administration of sulfonamide compounds (sulfathiazole 24 Gm., sulfadiazine 6.5 Gm. and sulfanilamide 2 Gm.). The chemotherapy was employed after the removal of a ureteral calculus. The patient died quietly thirty-six days after the initial dose of sulfathiazole. At no time were any significant neurologic signs noted.

At necropsy diffuse cerebral and cerebellar changes were observed. In spite of the lack of clinical evidence of renal impairment, the parenchymal and vascular changes were similar to those produced in experimental studies on the sulfonamide drugs.

The authors conclude that, though some of the cerebral and cerebellar changes observed were similar to those seen in patients whose death was preceded by various severe illnesses, the presence of renal changes characteristic of sulfonamide intoxication suggested that the cerebral and cerebellar changes resulted from sulfonamide therapy.

GUTTMAN, Philadelphia.

BACTEROIDES INFECTIONS OF THE CENTRAL NERVOUS SYSTEM. WILLIAM E. SMITH, ROBERT E. MCCALL and THOMAS J. BLAKE, Ann. Int. Med. **20**:920 (June) 1944.

Smith, McCall and Blake report 4 cases of infection of the central nervous system with an organism of the bacteroides group. In 2 cases meningitis and in 2 cerebral abscess was present. The authors found data in the literature on 11 fatal cases of infection of the central nervous system with Bacteroides.

Infection of the central nervous system due to Bacteroides arises most commonly from chronic otitis media, usually associated with mastoiditis. It is more frequent in adults, and its symptoms correspond to those associated with other pyogenic infections of the central nervous system. The onset of Bacteroides meningitis is acute, with elevation of temperature, headache and stiffness of the neck. The onset of cerebral abscess due to an organism of this group is less acute and may be signalized only by headache and vomiting. In cases of cerebral abscess, the cerebrospinal fluid may be clear. In cases of meningitis, the fluid is cloudy; the cell count ranges from 2,000 to 45,000 cells per cubic millimeter, and the sugar content is decreased, but the protein content is increased. The diagnosis depends on cultivation of the organisms—anaerobic, gram-negative, non-spore-bearing bacilli. Anaerobic cultures should be made in cases of meningitis or cerebral abscess, especially of otitic origin, when gram-negative bacilli are seen in smears or when no organisms can be cultivated aerobically. Primary isolation of bacteroides is greatly facilitated by addition of 30 per cent ascitic fluid to the medium. The course may be acute, with death occurring between the fourth and the ninth day in fatal cases. Recovery, when it occurs, may be prompt or prolonged, depending on the severity of the meningitis and the presence or absence of cerebral abscess.

On the basis of the cases already reported in the literature, the prognosis appears hopeless. However, 3 of the authors' 4 patients recovered. The authors state that the three factors which may have aided in recovery were more adequate surgical and supportive treatment and sulfonamide therapy. The treatment of choice, at present, consists of early and adequate surgical procedures to remove foci of infection in the ear and mastoid; repeated lumbar punctures for drainage of fluid, in cases of meningitis; appropriate measures for drainage of cerebral abscess; attention to indications for intravenous administration of fluids and transfusions, and sulfadiazine therapy.

GUTTMAN, Philadelphia.

MÉNIÈRE'S DISEASE. J. R. LINDSAY, Arch. Otolaryng. **39**:313 (April) 1944.

Lindsay examined the temporal bones of a middle-aged man who had had Ménière's disease for three years. During an attack of vertigo he fell, sustained a fracture of the skull and died of subdural hematoma. The temporal bones were fixed in a solution of formaldehyde and prepared in the usual way. The left bone was serially sectioned in the vertical plane, and the right bone was sectioned horizontally. The pathologic changes in the right ear were limited to the vascular congestion and hemorrhage in the modiolus and to the degenerative changes in the spiral ganglion. The former were due probably to the cranial trauma, while the changes in the ganglion were thought to be related directly to the hearing loss for tones above the frequency of 2048 cycles.

On the left side, the membranes of the internal ear were well preserved. The cochlear duct was greatly dilated, and beginning herniation of the duct through the helicotrema was observed. There was degeneration of cells of the spiral ganglion in the basal coil. The ductus reuniens was of normal size. The saccule almost completely filled the vestibule, and the wall of the saccule overlay the stapedial foot plate. The utricle was dilated in the lower portion leading to the ampulla of the posterior canal, where a tendency to herniate behind the thick wall of the ampulla was seen. The walls of the semicircular canals were normal.

The cause of the hydrops was not evident on histologic examination.

RYAN, M. C., A. U. S.

HEMANGIOBLASTOMA OF THE MEDULLA (LINDAU'S DISEASE). MERVYN H. HIRSCHFIELD, J. Nerv. & Ment. Dis. **99**:656 (May) 1944.

Lindau's disease is characterized by retinal angiomatosis and by hemangioblastomas of the cerebellum, brain stem and spinal cord, with cyst formation and syringomyelia. Cystic areas occur in the pancreas, kidneys and liver. Hirschfield reports the case of a man aged 21 with von Hippel's disease in whom signs and symptoms of medullary involvement developed. He was treated with radiation, receiving a total of 1,475 r in twenty-six days, with remarkable improvement in the neurologic signs.

CHODOFF, Langley Field, Va.

CENTRAL NERVOUS SYSTEM COMPLICATIONS ARISING FROM DISEASES OF THE BLOOD FORMING TISSUES. STACY R. METTIER, J. Nerv. & Ment. Dis. **99**:758 (May) 1944.

Mettier reviews the clinical manifestations referable to the central nervous system in a large series of cases of various diseases of the blood-forming tissues. In treatment of the neurologic aspects of pernicious anemia, early and vigorous liver therapy is essential, and it will produce considerable improvement in three to six months. Certain malignant neoplastic processes involving the hematopoietic structures may give rise to pressure symptoms within the central nervous system. Of these, Hodgkin's disease and lymphosarcoma are the most important, with an incidence of neurologic complications, of various sorts, of 10 to 14 per cent. In 20.5 per cent of a series of 334 cases of leukemia neurologic symptoms were present. The author has seen several instances of a Ménière type of vertigo due to leukemia. Diseases characterized by hemorrhagic diathesis may be marked by subarachnoid or intracerebral hemorrhage. Four cases of this type were observed with thrombocytopenic purpura. Severe anemia due to rapid loss of blood may be complicated by focal convulsions, due either to the fall in blood pressure or to the irritating effects of anoxemia on the cortical cells.

CHODOFF, Langley Field, Va.

Vegetative and Endocrine Systems

THE MORGAGNI-STEWART-MOREL SYNDROME: REPORT OF A CASE WITH PNEUMOENCEPHALOGRAPHIC FINDINGS. MATTHEW T. MOORE, Arch. Int. Med. **73**:7 (Jan.) 1944.

Moore reports the case of a 39 year old woman whose difficulties consisted of seizures, double vision, headaches, periods of disturbance in gait and clumsiness and, perhaps, a mild menstrual abnormality. During the patient's hospitalization it was reported that the mood varied from depression to euphoria. There were no gross abnormal neurologic signs. Roentgenograms of the skull revealed a thickened calvaria, with frontoparietal hyperostosis frontalis interna and calcification in the falx. Pneumoencephalographic examination revealed pronounced cortical atrophy over the frontal and parietal lobes, atrophy of the islands of Reil and moderately advanced internal hydrocephalus, with asymmetry and irregularity of the lateral ventricles.

The condition is regarded as the Morgagni-Stewart-Morel syndrome.

GUTTMAN, Philadelphia.

ADRENAL CORTICAL FUNCTION INDEPENDENT OF DIRECT NERVOUS ACTION: A NEUROLOGICAL STUDY OF NORMAL, DENERVATED AND TRANSPLANTED ADRENAL GLANDS OF ALBINO RATS. W. E. MACFARLAND, J. Exper. Zool. **95**:345 (April) 1944.

In 10 animals, wallerian degeneration within the adrenal gland after excision of the greater and lesser splanchnic nerves produced marked changes in the medulla but no detectable cytologic changes in the cortex.

In 48 animals, the left adrenal was transplanted to the left inguinal region. The animals were divided into two groups. In 8 rats of one series, the transplant was recovered as a small nodule of cortical tissue. In the other 24 rats the right adrenal was removed five to three hundred and seven days after transplantation of the left adrenal. Fifteen of these animals died from one to fifteen days after the operation, and the transplants were removed from the 9 survivors from six to forty-two days after loss of the right adrenal gland.

The functional activity of the transplants was shown by the survival of the animals and by their changes in weight after each operation. Bilateral adrenalectomy in rats of this stock produced death in one to seventeen days.

Microscopic examination of serial sections of normal adrenal glands showed a few small bundles and scattered fibers of nerves passing, without branching, through the cortex to terminate in the medulla. Examination of functional transplants showed robust masses of cortical tissue which were lacking in medulla or any detectable nerve content.

Regeneration was most effective when (*a*) the whole left adrenal was transplanted and (*b*) the right adrenal gland was left in situ for not longer than ten days before removal. About 69 per cent of the glands transplanted in toto showed functional regeneration.

Ganglion cells were not noted in the cortex but were observed in the medulla in about 50 per cent of all the adrenals examined. Ganglion cells may be more abundant in the right than in the left adrenal gland. All the evidence indicates that the medulla of the adrenal gland is the only part which is innervated by secretory fibers and that there is no direct neural control of the functional activity of the cortex.

REID, Boston.

RETURN OF VIRILITY AFTER PREFRONTAL LEUCOTOMY, WITH ENLARGEMENT OF GONADS. R. H. HEMPHILL, Lancet **2**:345 (Sept. 9) 1944.

Hemphill reports the case of a man aged 33 with an obsessional neurosis, which had increased in severity since the first symptoms appeared, at the age of 23. He had been sexually potent but had lost his libido and became impotent at the age of 28. He had lost weight, owing to a highly inadequate intake of food. His testes were tiny and soft on admission, and the penis was thin and long. There was little hair on the body, and it

was falling out on the pubis. Biopsy of the testes showed shrunken tubules, hyalinization of the basement membrane, loss of seminiferous epithelium, absence of mature sperm forms and no compensatory hyperplasia of interstitial cells. Excretion of 17-ketosteroids was 3.8 mg. per twenty-four hours. Protracted attempts to increase his weight failed, and eighteen months later a prefrontal leukotomy was performed. The day after operation his appetite showed great improvement, and he gained weight rapidly. His penis became longer and thicker; the testes became large and firm and descended noticeably, and the scrotum developed to accommodate them. All his obsessions disappeared, and he became good natured and complacent, though a bit lazy. Four months after operation he had normal libido and potentia. The output of 17-ketosteroids rose to 8.87 mg. per twenty-four hours. He married and held a position as a clerk.

Since the weight and atrophy of the genitalia had remained unchanged for years prior to operation, in spite of other therapy, Hemphill feels certain that the change can be attributed entirely to the surgical procedure. He states that perhaps frontohypothalamic, as well as thalamic, pathways were interrupted, thus serving to release pituitary inhibition of the gonads.

McCarter, Boston.

Treatment, Neurosurgery

Surgical Management of Compound Depressed Fracture of Frontal Sinus, Cerebrospinal Rhinorrhea and Pneumocephalus. E. S. Gurdjian and J. E. Webster, Arch. Otolaryng. **39**:287 (April) 1944.

Over a twelve year period (1930-1942) Gurdjian and Webster treated 31 patients with compound depressed fracture of the frontal sinus and in its neighborhood, 13 with cerebrospinal rhinorrhea and 9 with pneumocephalus.

Compound depressed fracture of the frontal sinus and its neighborhood may establish a communication between the nose and the cranial cavity. Hence, it is a potential source of infection, and the rationale of operative intervention is to repair the communication between the intracranial cavity and the nasal spaces and thus to obviate the possible contamination of the former.

Automobile accidents rank far ahead of other sources of trauma in producing compound depressed fractures in this region. The fractures of about 75 per cent of the 31 patients were due to motor accidents. Seven patients in the group were not rendered unconscious at the time of their injury; 13 gave a history of a short period of unconsciousness, and 11 had evidence of severe damage to the brain. Twenty-one patients in the group had dural tears, varying from small punctures to extensive lacerations. In fully one half of these persons there was underlying lacerated and necrotic brain tissue. Cerebrospinal rhinorrhea occurred in 4 patients, and pneumocephalus was observed in 3 patients. Meningitis developed in 3 patients, 2 of whom recovered. Brain abscess occurred in 1 patient and was successfully treated. Three of the group of 31 patients died, 2 as a result of associated damage to the brain and 1 as a result of meningitis.

Compound depressed fracture in the region of the frontal sinus should receive surgical treatment as soon as the condition of the patient permits. Careful roentgenographic examination should precede every operative repair, so that the extent of bony damage may be carefully evaluated before operation. The authors prefer exposing the lesion by extending the initial laceration in an appropriate manner. In some cases a frontotemporal skin flap is made. The comminuted pieces of bone are removed from the outer wall of the frontal sinus. The interior of this sinus is then carefully inspected, and comminuted and depressed pieces, if present, are removed. Dural tears are repaired with silk. If the necrotic brain tissue is found in the sinus, it is sucked away. If the tear in the dura is beyond repair, the edges are approximated and held together with sutures, and the area is packed with antiseptic gauze to hold the dura away from bony attachments. The pack may be removed slowly over a period of six to eight days, or the wound may be closed completely and six to eight days later reopened for removal of the pack. In the absence of local infection, repair of the bony defect may be undertaken four to six months after the accident. If postoperative infection occurs, the defect may be repaired eight to ten months after the infection has completely cleared up. In repairing the defect, osteoperiosteal transplants or a plastic substance called "plexiglas" may be employed.

Traumatic cerebrospinal rhinorrhea is a serious complication of head injury, even with the availability of chemotherapeutic drugs. It is probably more common than is observed or described, as the leakage may not be detected because of the patient's prone position in bed. The condition is serious because infection may enter the cranial cavity from the nasal passages. Meningitis and cerebral abscess are common sequelae. Healing of acute cerebrospinal rhinorrhea, with no reappearance of leakage, may take place during absolute rest in bed. When it recurs on one or more occasions, closure of the fistulous tract without operative intervention is rare, and meningitis or abscess of the brain or both may develop months or even years after the accident. In such cases treatment is difficult, and frequently death results.

Of the 13 patients reported, 8 were seen in the acute stage of trauma to the head, and 5 had recurrent cerebrospinal rhinorrhea. Of the patients seen during the acute phase, 4 had surgical treatment, and the remaining 4 were treated conservatively. The indication for operation on 3 patients was the presence of a compound depressed fracture of the frontal sinus and in its neighborhood. The other patient receiving surgical treatment had a comminuted fracture of the inner wall of the frontal sinus and of the cribriform plate, with no laceration of the forehead. Treatment may be conservative or operative or both. If a conservative measure is decided on, the patient is strictly confined to bed and is given prophylactic doses of sulfonamide compounds. If operative management is desirable, the problem varies according to the type of condition. In a case of compound depressed fracture, the initial wound may be enlarged by appropriate extension, the area of damage exposed and the torn dura repaired. In a case of recurrent rhinorrhea with no complications, the anterior fossa may be exposed by turning a low frontal flap. The torn dura is then exposed externally and repaired. When a complicating condition is already present, treatment is directed first to the complication, before repair of the cranionasal fistula is considered.

Pneumocephalus may be present without cerebrospinal rhinorrhea, and many patients with cerebrospinal rhinorrhea have no associated pneumocephalus. The usual avenue of entrance of air is a cranionasal fistula. Fracture through the petrous bone is the second avenue of entrance, with bloody or cerebrospinal otorrhea as a sequela. In 4 patients in this group, pneumocephalus was associated with cerebrospinal rhinorrhea, and in

4 others, with cerebrospinal or bloody otorrhea. In 1 patient a compound depressed fracture of the occipital region which had been left untreated for five days was the avenue of entrance of air. The air may be subdural, ventricular, intracerebral or subarachnoid. Most commonly it is subdural, while subarachnoid accumulation is rare. Diagnosis is simple after roentgenographic examination.

Conservative treatment, namely, strict rest in bed in a semi-Fowler position, has a definite place in the management of pneumocephalus associated with acute injury of the head. For the acute form of pneumocephalus, operative intervention may be indicated because of the presence of compound depressed fracture in the neighborhood of the frontal sinus or elsewhere. Pneumocephalus appearing months or years after the acute injury is treated surgically. Usually latent pneumocephalus is due to a cranionasal fistula. If the fistula extends through the anterior fossa, an adequate frontal bone flap may be used to explore the region extradurally and intradurally.

RYAN, M.C., A.U.S.

REPAIR OF PERIPHERAL INJURIES OF THE FACIAL NERVE. R. C. MARTIN, J. Nerv. & Ment. Dis. **99**:755 (May) 1944.

Early attempts at repair of the peripherally injured facial nerve utilized the hypoglossal and spinal accessory nerves for the proximal segments and the facial nerve for the distal portion. If no proximal segment of the facial nerve can be found, this operation is useful, although distressing associated movements occur. Bunnell, in 1927, performed a successful end to end suture of the facial nerve by removing the intratympanic portion of the nerve from its bed and shifting it anteriorly. Homologous sensory or motor grafts have been used as bridges by which the axons gain access to the distal facial trunk. End results in patients treated by these methods show no contractures, but there remain associated movements when strong volitional movements are attempted. Function of the frontalis muscle is seldom regained.

CHODOFF, Langley Field, Va.

PREVENTION OF FATALITY AND FRACTURE DURING ELECTRICAL COMA THERAPY. HARRY F. DARLING, J. Nerv. & Ment. Dis. **100**:70 (July) 1944.

Darling believes that the best results in avoiding skeletal fractures as complications of electric coma therapy are to be obtained by allowing the limbs to convulse freely rather than by applying manual or mechanical restraints. More than 350 courses of treatment have been given with this method without direct or indirect fatality or fracture. Since no attempt is made to impede the freedom of action of epileptic patients during their seizures, the attempt to restrain persons with artificially induced fits seems unwarranted.

CHODOFF, Langley Field, Va.

Congenital Anomalies

FAMILIAL CEREBRAL DEGENERATION WITH CORTICAL ATROPHY. H. M. KEITH, Proc. Staff Meet., Mayo Clin. **18**:499 (Dec. 15) 1943.

Keith performed encephalographic studies on 2 infant siblings. Gross encephalic abnormalities were observed; therefore a diagnosis of diffuse cortical atrophy with progressive mental retardation was made for both infants.

GUTTMAN, Philadelphia.

A CASE OF PARTIAL CONGENITAL HEMI-HYPERTROPH. A. HUSE, J. Neurol., Neurosurg. & Psychiat. **7** (Jan.-April) 1944.

Huse reports the case of a feebleminded man, aged 3 who showed enlargement of the entire left side of th body, involving both osseous and muscular tissues. Th hypertrophied left side was weaker than the right. The condition was associated with signs of Recklinghausen disease. The author concludes that two congenital anomalies were present and that the mental deficiency was either idiopathic or secondary to the congenital anomalies.

N. MALAMUD, Ann Arbor, Mich.

CYCLOCEPHALON AND HYPERTROPHIED STRUCTURES IN THE BRAIN OF A CHILD WITH MULTIPLE FACIAL MALFORMATION. JULIO ARANOVICH, Rev. neurol. de Buenos Aires **8**:312 (July-Sept.) 1943.

A male child died on the seventh day of life, with hyperthermia. Except for congestion of the liver, spleen and lungs, autopsy revealed nothing abnormal in the internal organs. Microcephaly, microphthalmia on the left side and multiple chondromas of the face were present.

Macroscopic examination of the brain showed pronounced malformation of both cerebral hemispheres. They formed a large, single vesicular structure, with absence of fissuration and depressions on the lateral surfaces in the region of the sylvian fissure. There was slight indentation at the anterior extremity of this vesicle, at the site of the interhemispheric fissure.

At the base there was typical arhinencephaly, with absence of the olfactory bulbs, nerves and tracts; there was only one ventricle and no corpus callosum; a diverticulum from the roof of the third ventricle pushed the anterior part of the vermis posteriorly; the pyramidal tracts were entirely absent; the anterior part of the vermis and the dorsal nuclei of the thalamus were poorly developed; there was complete absence of th optic radiations and olfactory pathways; the cerebra cortex was arrested in development, the stage corre sponding to that usually seen in the second month o fetal life; there was complete absence of association commissural or projection fibers in the cerebral cortex the region of the cornu ammonis was the most normally developed part of the brain on either side, and th olives, red nuclei and hypothalamic region were hyper trophied.

The author believes that arrest of development of the neoencephalon permitted inordinate growth of paleoencephalic structures. He postulates a disturbance in circulation of the cerebrospinal fluid in the first to the third month of fetal life to account for the bulge in the roof of the third ventricle and the arrested development of the cerebral cortex.

SAVITSKY, New York.

Encephalography, Ventriculography, Roentgenography

VENTRICULAR CHANGES AFTER CLOSED HEAD INJUR H. DAVIES and M. A. FALCONER, J. Neurol. Psychiat. **6**:52 (Jan.-April) 1943.

Davies and Falconer report the results of pneumoencephalographic studies in 100 cases of closed head injury. The cisternal route of injection was used in preference to the lumbar, and only small quantities o air (30 to 60 cc.) were injected. The diagonal width of the body of the ventricle was used as a criterion of the size of the lateral ventricle, a diameter of more

than 2 cm. or a difference of 2 mm. between the ventricles being considered abnormal. A series of 50 controls were studied for comparison. Enlargement of the ventricles, either focal or generalized, unilateral or bilateral, was found in 69 of the 100 cases. The frequency of such dilatation tended to increase with the severity of the trauma, as measured by the duration of post-traumatic amnesia or the presence of blood in the cerebrospinal fluid. Ventricular enlargement first appeared within two to three weeks after injury and reached its maximum within a month. The dilatation, especially of the focal type, was less influenced by the site of the direction of the violence than by the presence or absence of localized fracture of the skull. There was in the majority of cases a close correlation between the clinical signs and the encephalographic changes. This was most striking in cases with residual signs of pyramidal involvement on one side of the body, in which the contralateral ventricle was usually dilated. In cases of post-traumatic intellectual deterioration the ventricles were also frequently enlarged. However, post-traumatic syndrome, post-traumatic epilepsy, signs of primary involvement of the hypothalamus and brain stem and cranial nerve palsies were usually not associated with ventricular dilatation. Thus a normal encephalogram does not rule out permanent organic damage. The authors do not attach significance to nonfilling of the ventricles with air. The mechanism of ventricular dilatation appears to be due to intracerebral atrophic processes resulting either from a focal traumatic lesion or from a generalized vascular disturbance rather than from obstruction to the cerebrospinal fluid pathways.

MALAMUD, Ann Arbor, Mich.

Diseases of Skull and Vertebrae

INJURIES OF THE FACIAL PORTION OF THE SKULL IN WARTIME AND IN PEACETIME. F. SPECHT, München. med. Wchnschr. 89:391 (May 1) 1942.

Specht emphasizes that the facial portion of the skull encloses a complex cavity which is of considerable functional importance. The rhinologist should make the diagnosis and decide on the treatment. Intracranial complications and septic conditions may result from nasal infection under normal circumstances and even more frequently after injuries. Early prevention of adhesions and of obstruction of the accessory cavities is of the greatest importance. Recovery in cases of severe osteomyelitis originating from accessory cavities may be obtained by radical surgical intervention. Immediate correction is more simple and less dangerous. Internal healing may be obtained only by rhinologic methods. Involvement of adjacent or of more distant organs should be kept in mind. Fractures of the basal part of the skull with aural involvement are frequent. There are also less common paths of infection, such as the subperiosteal abscess of the temporal bone or of the zygomatic arch resulting from suppuration of the middle ear. Whether or not the injured patient will get the correct treatment depends on competent organization, which, however, need not be of vital importance provided the physician who is first called will consult with all the specialists concerned as soon as possible.

J. A. M. A.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

RALPH E. HAMILL, M.D., *in the Chair*

Regular Meeting, Oct. 10, 1944

Degeneration of the Basal Ganglia Due to Chronic Carbon Disulfide Poisoning in Monkeys. DR. RICHARD B. RICHTER.

Four monkeys (Macaca mulatta) were repeatedly exposed to carbon disulfide vapor over periods of three hundred and sixty-four to seven hundred and thirty-six days. Acute intoxication was avoided. All the animals manifested signs indicative of profound cerebral damage. These were interpreted as chiefly extrapyramidal in origin. Most striking were certain motor disturbances common to all of the monkeys. The animals became progressively inactive; mimetic facial movements disappeared, and many reactions of orientation, flight and defense were lost. Walking and climbing became slow, difficult and incoordinated, without actual paralysis. The head, trunk and extremities assumed postures of extreme flexion with plastic rigidity. Pronounced action tremors appeared in all animals, and tremor of the resting extremities was present in 1 animal. There were impressive resemblances to the akinetic-rigid syndrome of parkinsonism.

Pathologically, the essential changes in 3 of the animals were massive necrobiotic lesions, symmetric on the two sides and confined strictly to the globus pallidus and the substantia nigra. These had destroyed virtually all the pallidum and the zona reticulata of the substantia nigra. In the fourth animal there were numerous scattered destructive lesions in the corpus striatum and the pallidum, as well as in the substantia nigra.

The pathogenesis of the lesions and their relation to the animals' symptoms and to certain cases of chronic carbon disulfide poisoning in man were discussed.

DISCUSSION

DR. FREDERICK HILLER: Dr. Richter is to be congratulated on this splendid experimental work. On seeing his instructive slides, I was reminded of what I described about twenty years ago as the effect of carbon monoxide poisoning on the human brain. Symmetric necrosis of the pallidum is regarded as a typical effect of such poisoning. This necrosis is not limited to the pallidum but, among other sites in the brain, is also found in the substantia nigra, where the lesion is more or less limited to the so-called red, or reticular, zone. I wonder whether Dr. Richter found this to be true in his experimental animals.

The predilection of the necrosis for certain areas of the brain has puzzled all who have examined the brain in cases of this type. My associates and I were inclined to attribute this predilective localization to a vascular factor, although we did not feel quite satisfied in pronouncing specific circulatory disturbances as the exclusive basis of the pathoclisis in this condition. It is, of course, difficult to deduce from an advanced stage of necrosis whether stasis or some other circulatory failure has caused the cerebral lesion, which presents all the characteristics of tissue necrosis, with vast numbers of gitter cells and predominantly mesodermal repair. In his experiments, Dr. Richter has been in the much more favorable position of seeing the initial stages of this reaction of the brain. I should like to ask whether he has formed any conclusions about the nature of this type of encephalopathy.

DR. VICTOR E. GONDA: The gross pathologic changes localized almost entirely in the striatal system have been mentioned, as well as the minor alterations, which were rather widespread. May I ask whether any changes were seen in the cortex, especially in the so-called motor and premotor cortex?

My second question is a purely theoretic one. Does Dr. Richter think that, under the same experimental conditions, higher apes would show more outward manifestations of the parkinsonian syndrome than monkeys?

DR. GEORGE B. HASSIN: The changes so well presented by Dr. Richter, which he classified as necrosis and which I should prefer to call softening, are not specific for carbon disulfide poisoning, for they may accompany poisoning with other substances, especially carbon monoxide. A definite diagnosis from the microscopic examination alone is thus not possible. I was glad to hear that Dr. Hiller is giving up his vascular theory of the changes associated with carbon monoxide poisoning, a hypothesis advocated also by Spielmeyer and his followers. Dr. Richter's slides showed that the condition of the blood vessels, many of which appeared newly formed, could not be held responsible for the scattered, diffuse alterations in the brain. The changes are most likely due to a direct action of the poison on the ganglion cells, glia, nerve fibers and blood vessels. They seem to involve the peripheral nerves. Probably because of lack of time, Dr. Richter did not mention the changes, if any, in the cortex. It seems that with carbon disulfide poisoning, as with any other type of poisoning, the entire nervous system is involved, the basal ganglia being affected more than any other portion.

DR. R. P. MACKAY: The striking feature of this work is undoubtedly the close resemblance between the pallidal degeneration in these cases of carbon disulfide poisoning and that seen as a result of exposure to carbon monoxide. It is generally admitted that carbon monoxide produces its effects by inducing anoxia. If one places an animal under 5 atmospheres of oxygen, one may saturate the blood with carbon monoxide without damaging the brain, since sufficient oxygen is carried in solution in the blood plasma for the needs of the animal. This being true, it behooves one to ask whether the changes following carbon disulfide poisoning may not also be due to anoxia.

Did Dr. Richter study the oxygen content of the blood in his monkeys or carry out other observations on the ability of the blood to carry oxygen? Conceivably, carbon disulfide, a fat solvent, might dissolve the envelope of the red blood cell and destroy the hemoglobin.

DR. RICHARD B. RICHTER: In answer to Dr. Hiller: These preparations do not resemble the pathologic effects of experimental carbon disulfide poisoning previously described in other species, except in 1 cat of Ferraro's, in which the lenticular nucleus was reported to be necrotic. What they do resemble, almost exactly,

are the necrotic lesions of carbon monoxide poisoning in man, those of experimental carbon monoxide poisoning in dogs and the necrotic areas described by Hurst in the cortex, subcortical white matter, cerebellum and basal ganglia of monkeys after repeated sublethal doses of potassium cyanide. Although the period of intoxication in the animals was prolonged, the lesions themselves are relatively acute and appear to have developed as the cumulative effect of repeated small insults, from which finally the tissues could not recover.

I do not think this material offers the answer to the nature or pathogensis of these, or similar, toxic degenerations or necroses. The completeness of the necrosis and the presence of proliferation and other vascular changes within the lesions themselves suggest a vascular origin. But there are other considerations which speak strongly against such a mode of development. The complete absence of vascular alterations, even of engorgement and stasis, in all other areas of the brain does not support the theory of either structural or functional vascular pathogenesis. Furthermore, it is inconceivable to me how lesions which exhibit such perfect symmetry as these do, and are so exquisitely selective for certain gray structures, could depend on vascular changes. For instance, in the 1 animal in which the corpus striatum was affected, there was pronounced destruction of the small bridges of gray matter which unite the caudate nucleus and the putamen across the internal capsule without the capsule itself being affected in the least. How a vascular lesion could be as selective as that is difficult to understand. The material appears to fit Vogt's concept of general pathoclisis—only this means very little. Whether the preeminent vulnerability of the globus pallidus and substantia nigra is a vulnerability to carbon disulfide as such or to anoxia, or whether it is concerned with effects on respiratory enzymes in the nerve cells is not known.

It is of great interest that, just as in Dr. Hiller's case of carbon monoxide poisoning with damage to the substantia nigra, it was the zona reticulata of the substantia nigra which showed the predominant damage.

In reply to Dr. Hassin: The brains of all these animals were examined in serial sections from the frontal to the occipital pole. In all there was some degree of cellular change in the cortex of the frontal lobes, especially in their most rostral parts. Even these small changes were not seen in the motor cortex or caudal to it. I do not believe that this relatively insignificant amount of neuronal damage was functionally significant, at least not for the motor syndrome exhibited by the animals.

Toxoplasma Encephalomyelitis: A Clinical Pathologic and Experimental Study. DR. DOUGLAS BUCHANAN and DR. CARLOS LARA-GONZALES.

1. A clinical report was given of 8 cases of Toxoplasma encephalomyelitis with chorioretinitis.

2. A pathologic report was given of 3 cases in which autopsy was done.

3. The history of recognition of this disease in man was reviewed.

4. The clinical picture of this disease in its prenatal, infantile and adult forms was described.

5. Attempts to cultivate the organism were reported. Experimentally, it was found possible to culture the toxoplasma on the allantoic membrane of fertile hens' eggs and to pass the organism through six generations. It was found impossible to culture the organism on any truly artificial medium.

Attempts were made to produce a pure culture of the toxoplasma from the peritoneal exudate obtained from infected mice. Methods of controlled sedimentation and controlled centrifugalization were employed, but these failed.

Attempts were also made to culture the organism by control of the p_H of the infected suspension with various chemical agents, but these attempts failed. These experiments were carried out with the hope of producing a pure culture of toxoplasmas which could then be used in a cutaneous test for evidence of the infection in man.

6. Studies were made of the life cycle of the organism; mice, rabbits, chickens, ducks and hamsters were used. When these animals were given intraperitoneal and/or intracerebral injections of the toxoplasma, no evidence of the organisms in the peripheral blood was found at any time before the animal's death or its recovery.

When the toxoplasma was injected intravenously, a few organisms were observed in the peripheral blood of 4 mice just before death. In all the other animals no organisms were found at any time before the animal's death or recovery. The peripheral blood of these animals was examined by direct smear every three hours until death or recovery. Although evidence of the toxoplasma was found in the peripheral blood in only 4 mice, the organism was noted in the organs of all the animals after death. In addition, transmission of the disease to other groups of animals was obtained with suspensions of these organs.

7. The present method of testing human serum for the presence or absence of neutralizing antibodies to the toxoplasma was described.

8. The significance of this disease in the production of spastic quadriplegia, mental retardation and convulsions was pointed out.

DISCUSSION

DR. GEORGE B. HASSIN: I think this form of encephalitis was present in a newborn infant, a twin, who died fifteen days after birth. I did not have a good history, but I obtained the brain and demonstrated the pathologic findings before this society (Acute [Epidemic?] Encephalitis: Report of a Case in a New-Born Twin with Histologic Observations, ARCH. NEUROL. & PSYCHIAT. **18**:44 [July] 1927). The usual changes seen with encephalomyelitis were present; in addition, there were peculiar bodies, the nature of which I did not understand. Under the influence of the work of the British neuropathologist, De Fano, I classified them as "minute bodies." Some are single; others are clumped together and are, in my opinion, identical with the formations described twelve years later by Wolf and Cowen and subsequently identified by them as toxoplasmas. I sent photographs of my histologic specimens to Dr. Abner Wolf and Dr. Sabin, who could not commit themselves without seeing the slides. These I could not send, as they mysteriously disappeared, together with the gross material. Dr. Buchanan rightly stated that the micro-organisms obtained in cultures and in experimental work differ from those seen in histologic specimens, and he probably can help me in identifying them in my slides. I think my case was one of toxoplasmic encephalitis. I was particularly interested in this case as the disease occurred in a twin, while the other twin and the mother remained well. A similar case in a twin was recorded by Zuelzer (Infantile Toxoplasmosis, with Report of Three New Cases, Including Two in Which the Patients Were Identical Twins, *Arch. Path.* **38**:1 [July] 1944).

DR. PETER BASSOE: Within the last three weeks I have seen 2 adults with chorioretinitis close to the optic disk. An ophthalmologist diagnosed the condition as the "juxtapapillitis" described by Jensen in 1908. I looked up this article, and the picture was similar to that in the case Dr. Buchanan described. I also looked up other articles on Jensen's disease, and all state that no satisfactory cause has been found. There have been guesses, but no proof, that tuberculosis, syphilis and other conditions are responsible. Perhaps the toxoplasma is the answer.

DR. VICTOR E. GONDA: I had an opportunity to study roentgenograms of the skulls of 2 children between the ages of 1 and 2 years in which extensive calcifications were shown. These calcifications are considered so characteristic of the disease that their presence constitutes verifications of the diagnosis of toxoplasma encephalitis. Will Dr. Buchanan interpret these observations?

DR. DOUGLAS BUCHANAN: I agree with Dr. Hassin that the organisms in his case were toxoplasmas; those at 7 and 11 o'clock I could not identify.

Of our 63 patients who had had trouble with their eyes and whose serum gave positive reactions for the toxoplasm, and, in addition, of 11 patients who presented the complete picture of toxoplasmosis, only 1 showed calcifications in the skull. However, these were in a unique position; all appeared to be in the posterior part of the brain. This localization is used in the differential diagnosis of toxoplasmosis and tuberous sclerosis.

Causalgia: A Preliminary Report of Nine Cases in Which Treatment with Surgical and Chemical Interruption of the Sympathetic Pathways Was Successful. CAPTAIN I. JOSHUA SPEIGEL and CAPTAIN JACK L. MILOWSKY, Medical Corps, Army of the United States.

From an analysis of the clinical picture and of the results following treatment of 9 patients with causalgia observed by the authors in an unselected series of 275 men with peripheral nerve injuries, the following conclusions were drawn:

1. The syndrome followed injury to all or any of the major nerves of the upper extremity. In spite of numerous injuries to the veins of the lower extremity, only 1 case of causalgia involving the leg occurred.

2. Injury to a blood vessel frequently accompanies nerve injuries in cases of causalgia but is not a necessary concomitant of nerve injury in the production of pain.

3. The most constant symptom of causalgia is hot, burning pain, aggravated by movement and friction.

4. The most constant finding is shiny, cold, profusely perspiring and frequently cracked skin in the extremity involved, with hyperesthesia occurring in most cases. Roentgenographic evidence of decalcification of the involved extremity is frequently seen.

5. The pain does not appear to be due to continuous irritation by a scar or a foreign body.

6. The degree and quality of pain are in no way commensurate with the type and extent of injury.

7. The area of sensory deficit does not delineate the area of pain, but the two frequently shade into each other.

8. Personality disorders and hysteria are the result rather than the cause of causalgia.

9. Neurolysis is not a useful procedure in the treatment of causalgia per se, although it may be necessary in treatment of the specific nerve deficit.

10. It is injudicious to subject the patient to a series of operations ranging through neurolysis, nerve section and periarterial sympathectomy before attempting chemical and surgical interruption of the sympathetic pathways.

11. Interruption of the sympathetic pathway, temporarily, by sympathetic block, or permanently, by surgical sympathectomy, is a highly dependable form of treatment for causalgia. In case of the upper extremity, it is not necessary to remove the stellate ganglion for effective control of the pain.

12. Sympathectomy should not be performed until a series of diagnostic sympathetic blocks has proved the efficacy of interruption of the sympathetic pathway.

13. Occasionally the pain of causalgia can be more or less permanently controlled by sympathetic block with local anesthesia when sympathectomy, for other reasons, is not feasible. Alcohol block, in selected cases, is a useful procedure.

It is concluded, therefore, that sympathetic block by chemical or surgical means is a highly satisfactory method of treatment for causalgia and should occupy a prominent position in the therapeutic procedures of those whose function it is to treat this complaint.

DISCUSSION

DR. GEZA DE TAKATS: I congratulate Dr. Spiegel on this series. A few points should be emphasized. One should never consider doing a sympathetic ganglionectomy unless a sympathetic block is successful. A certain group of patients responds favorably. When the patient is seen early, sympathectomy, repeated sympathetic blocks combined with physical therapy or preganglionic sympathectomy is effective. But a time element militates against this procedure. Most of the patients seen after industrial accidents come years later, having consulted industrial surgeons, orthopedic surgeons, neurologists and so on. By the time they get to some one who can take care of them, they have been in splints for intractable pain; they have an addiction to morphine, and a syndrome has developed in which the continuous pain has stamped a pattern on the cortex. Interruption of peripheral nerves does not help this syndrome; and, while sympathetic block and sympathectomy are of value in the early stages, there comes a time, as Dr. Speigel has mentioned, when such treatment is not effective.

The second point is that there is a difference between the "hysterical hand" and the causalgic hand. The "hysterical hand" never shows any vasodilatation; if anything, it is cool, whereas the causalgic hand shows vasodilatation, which is certainly due to secretion of painful substances at the nerve endings. Why does sympathetic block or sympathectomy help when, obviously, the sympathetic nervous system has not been injured? Further work is necessary on this point.

This paper is stimulating, and I hope it will make every one feel the importance of treating these patients early.

DR. I. JOSHUA SPEIGEL: I wish to thank Dr. de Takats for his discussion. I should like, also, to reiterate one point: One should never think of performing a surgical sympathectomy without a repeated series of chemical blocks to determine whether or not it will be efficacious. I might add that chordotomy in cases of severe causalgia has not always been attended by relief of pain. Certainly, it is dangerous to try such a procedure in a case in which the cortical pattern of pain has already

been implanted. Of course we were fortunate. Our patients were young, and all the injuries were comparatively recent. The patients with long-standing causalgia, who have been permitted to stay in casts because of pain, are exceedingly difficult to treat. It is precisely for this reason that this paper is presented—to point out that direct chemical or surgical attack on the sympathetic nerve chain should be instituted early if a complete remission of symptoms is to be obtained.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

PAUL I. YAKOVLEV, M.D., *Presiding*

Regular Meeting, Oct. 19, 1944

Mental Deficiency as a Community Problem. DR. RANSOM A. GREENE, Waltham, Mass.

Close to 2 per cent of the total population falls within the limits of the definition of mental deficiency. Thus, in Massachusetts there must be about 100,000 people who are feebleminded. Of these, only about 10,000 are registered with the state and other public agencies and are known as feebleminded. Some 90,000, therefore, remain outside the official record. They represent a largely negative factor in the economic and political structure of the community. Of persons recorded as feebleminded, only about 5,000, or approximately 5 per cent of a total feebleminded population of the state, are in the institutions for the mentally defective. The Walter E. Fernald State School provides for 2,000 of them. There are between 5,000 and 6,000 persons who are recorded as feebleminded and should be in institutions but who remain in the community, in the care of their families and various social agencies. Some mental deficiency is preventable. The prevention is largely a matter of medical research in the field of mental deficiency. In a large proportion of cases idiocy and imbecility are due to preventable factors, such as prenatal hazards to maternal health, birth injuries, infections, nutritional deficiency and diseases of the brain in infancy and early childhood. To a considerable extent, moronity, inherited through defective germ plasm, is perhaps also preventable by eugenic measures. Yet feeblemindedness will still be produced by the unpredictable, and therefore nonpreventable, vagaries of transmission in the germ plasm of latent hereditary traits from apparently healthy and well endowed parents to some of their less fortunate offspring; and there will also always be persons who become disqualified for normal living and fall from borderline normal intelligence to the moron level as a result of the ever increasing dependence of modern man's social adjustment on his intelligence.

DISCUSSION

DR. WILLIAM G. LENNOX: The other day I read an article by Prof. L. H. Snyder, of Ohio, who has done a great deal of work on heredity. His experiments have shown that when the blood of one parent is negative for the Rh factor and that of the other is positive, feeblemindedness occurs in the children with unusual frequency. This factor contributes to clotting of the blood and causes damage to the brain. I wonder whether Dr. Greene has any information on this point.

DR. BRONSON CROTHERS: I should like to ask Dr. Greene what is his borderline between psychosis and feeblemindedness. I want to find an administrative criterion for the selection of children who can be handled in this school and those who cannot be handled in any institution for the feebleminded.

DR. RANSON A. GREENE, Waltham, Mass.: While heredity is a strong factor in mental deficiency, environment is also important. I know from available figures that in 1900 the average span of life in the United States was 49 years. In 1944, according to figures of insurance companies and to the statistics of the United States Bureau of the Census, the average span of life was almost 72 years. This means not only that the life span of healthy and well endowed people is increased, but that many who are potentially or actually feebleminded at birth are being salvaged. I wonder whether this does not mean that there is being salvaged a group of persons who will have to be cared for in an institution or carried around on a pillow just because they are alive. This group is increasing. The obstetricians and the pediatricians may be responsible in a measure for some of this. I think they should take into account certain factors that they have not considered seriously. I believe that a great deal of preventable mental deficiency results from environmental factors and that when more is learned about the causation of mental deficiency, it will be found that the most important factors are environmental, rather than hereditary.

In reply to Dr. Lennox' question about the Rh factor: I have read quite a bit on the subject, but I do not know much about it personally. I think it is a matter for research, which will lead somewhere in differentiation of what are hereditary and what are environmental influences. Many conditions probably involve both.

Dr. Crothers' question was pertinent and difficult. There is only one way I can answer it. This institution, which in three years will be 100 years old, was built and intended primarily for the care of the feebleminded, to educate them to the capacity of their intelligence. That is what it has always attempted to do. But as years have gone by, more and more applications are received for admission of children who are not capable of any measure of elementary scholastic or occupational training because their mental deficiency, obvious as it may be, is associated with a gross disorder in the development of their behavior pattern. The mental deficiency of these children is wholly a secondary problem. The major problem is the pattern of their behavior. Because of this, not only are they incapable of any measure of elementary scholastic and occupational training in a school for the feebleminded, but their presence in the group of trainable feebleminded children destroys the very purpose for which the school is primarily intended. Either this institution trains the feebleminded, or it cares for psychotic children who happen to be feebleminded as well, or who become deteriorated, i. e., demented. The latter task cannot be carried out on the plane of training for which the school was built. It is the task of a psychiatric hospital for children. There are feebleminded children who are also psychotic. They are noisy and destructive and will have to be cared for as long as they live. A certain number of morons as they grow older have dementia precox, or they had the disease primarily. They are not suitable for admission to an institution that cares for feebleminded children and expects to send at least some back to their homes or communities. One cannot send a psychotic and feebleminded child back to the community. Some of these psychotic children may be recognized as such in early childhood. There are no provisions for

their care at this school. They must go to a psychiatric hospital. There is no place in Massachusetts where a child with a psychosis can be cared for. I have begged for years for such an institution. Attempts have been made to care for them in some mental disease hospitals, but that does not work. Having been the superintendent of a psychiatric hospital myself, I know that it cannot be done. There should be a special place for the care of psychotic children.

Clinical Aspects of So-Called Mongolian Imbecility. DR. CLEMENS E. BENDA, Wrentham, Mass.

Among the various types of mental deficiency, mongolism is outstanding, for two main reasons: It is not due to hereditary factors and may therefore occur potentially in normal families; and, second, mongolism furnishes one of the most interesting illustrations of the way in which normal development can be influenced by abnormal environmental factors during the period of gestation.

In a recent study at the Boston Lying-in Hospital, Dr. Berkeley Beidleman found that a diagnosis of mongolism has been made in 42 cases since 1930, a figure which represents an average of 3.4 per cent of the births at that hospital for that period. Earlier estimates showed that mongolism occurs in at least 2 per cent of the births in the population, an incidence which certainly deserves the attention of members of the medical profession.

A study of the growth disorder after birth indicates that the child with mongolism lacks normal function of those glands which guarantee normal growth and maturation. There is evidence of hypofunction of the thyroid and the gonads and, to a minor degree, of the adrenal cortex. The pathologic changes suggest lack of thyotropic, gonadotropic and adrenocorticotropic hormones; this leads to the conclusion that the pituitary gland, which regulates these functions, is essentially at fault. From a study of the pituitary glands of more than 40 patients with mongolism evidence has accumulated that the pituitary of children with this condition is abnormal in many ways. It is beyond the scope of this presentation to discuss the abnormality of the pituitary in more detail.

It is evident, however, that the mongolian imbecile is born with mongolism and that the dysfunction of the pituitary is only part of the general developmental deficiency. The abnormality of the heart, so frequent in cases of mongolism; the pathologic changes in the vascular system; the abnormal lines in the hands, and many other factors indicate that the fetus was exposed to noxious factors during many months of the period of gestation and that the abnormality of pregnancy started soon after the impregnation of the ovum. The pathologic changes indicate a hormonal deficiency of the mother during pregnancy.

Studies were made on 250 mothers of children with mongolism, a number which has now been increased to more than 300, and the results checked by Dr. Beidleman, in his observations on the material of the Boston Lying-in Hospital. The results indicate that the mothers of these children were not in proper condition for pregnancy when they carried the child who proved to be a mongolian imbecile. Bleedings, abortions, prematurity and other factors indicate that mongolism occurs on a threshold of hormonal sterility. It is suggested that either the function of the corpus luteum or that of the pituitary is at fault during the specific pregnancy. A study of the factors producing the deficiency indicates that physiologic factors, such as age, or several pathologic conditions, such as illness, exhaustion and immaturity, may produce the temporary threshhold of sterility.

DISCUSSION

DR. BRONSON CROTHERS: Dr. Benda suggested that attempted abortion might produce mongolism. How early in the course of pregnancy would this have to occur? It seems to me that mongolian imbeciles are much alike.

DR. AUGUSTUS ROSE: By the threshold of sterility does Dr. Benda mean a physiologic or a pathologic condition of the mother?

DR. D. DENNY-BROWN: It is remarkable that the mongolian imbecile preserves a juvenile appearance, and thus differs notably from a child with progeria. If pituitary insufficiency is responsible for progeria, the thickness of the eyelids and the absence of wrinkling of the skin in mongolism would require additional explanation.

DR. BRONSON CROTHERS: On the theory that mongolism is an endocrine disorder, has Dr. Benda any explanation of such defects as congenital heart disease and congenital cataract?

DR. WILLIAM O. LENNOX: Does a woman ever have two mongoloid children? Does endocrine therapy offer any hope?

DR. CLEMENS E. BENDA, Wrentham, Mass.: In answer to Dr. Crothers' question about the time at which an abortion, or an attempted abortion, must occur to produce mongolism: My material includes several instances in which the child with mongolism was in the middle of a series of normal siblings. These cases appeared entirely unexplained. When I inquired into the circumstances of the pregnancy, several mothers told me confidentially that when they missed their first menstrual period, they took pills obtained from a drugstore to induce menstruation.

Another point worth noting is that in other cases of mongolism menstruation continued during the first three months of pregnancy, an indication that something was wrong with the mechanism of pregnancy. In a third group of cases a history of threatened abortion in the third month was given.

In regard to Dr. Crothers' question about congenital heart disease and congenital cataract: My theory is that all such deficiencies indicate a pathologic period of gestation. I think that the infantile development of the heart and vascular system of mongolian idiots is an indication of a general growth deficiency in fetal life. More recent research on cataract has produced evidence that congenital cataract is associated with various endocrine disorders of the mother or with infectious diseases during pregnancy.

Dr. Rose asked about the pathologic condition of the mother in relation to the threshold of sterility. My observations indicate that many mothers have difficulty in becoming pregnant, in spite of a desire to have children. Sometimes they have tried from five to ten years to have a child; and when they finally succeeded, the child was a mongolian imbecile. This has led me to suspect a hormonal deficiency of the mother, which may be related to inadequate function of the corpus luteum.

As to the offspring of persons with mongolism, there is no report in the literature which provides indubitable evidence that a woman with mongolism has borne a child. The only such report comes from an English source, but it is not accompanied with pictures and there is no proof that the woman under consideration really had mongolism. There are a number of people of East

European stock who have mongolian characteristics, and a feebleminded woman with these characteristics might easily be thought to have mongolism. I studied more than a dozen ovaries of women with mongolism, and in no case was there evidence of mature graafian follicles.

In answer to Dr. Denny-Brown's question about the relationship of mongolism and progeria: I am not able to give any facts. I have seen several cases in which premature aging was recognizable in young adults as a symptom of progressive deterioration; but I have seen only 1 case of true progeria, and I am not familiar with the details of the endocrine disturbance in that case.

In answer to Dr. Lennox, we have seen a few cases of 2 and 1 case of 3 mongolian imbeciles in one family. Such an occurrence is rare, however, and I should not hesitate to encourage a mother, if she is young enough, to have another child after having borne a mongolian imbecile.

Achondroplasia of Parrot and Marie and Familial Osteochondrodystrophy of Morquio: Demonstration of Patients. DR. LAWRENCE BOWSER, Waltham, Mass.

Three patients with the typical achondroplasia of Parrot (1872) and a sister and brother with familial osteochondrodystrophy, described by Morquio (1929), were presented and compared. The cases of the sister and brother were reported by Drs. Farrell, Maloney and Yakovlev (Morquio's Disease Associated with Mental Defect, ARCH. NEUROL. & PSYCHIAT. **48**:456. [Sept.] 1942). Familial osteochondrodystrophy has often been mistaken for achondroplasia; yet on comparison of these two types of dwarfism due to disorders of osteogenesis, the difference is striking. Aside from the fact that osteochondrodystrophy is a familial disease, several siblings being affected, although others in the same family may be normal, the skeletal abnormalities in this condition are of a different type and distribution than those seen in achondroplasia. In the latter condition the dwarfism is due to premature ossification of the epiphysial cartilages of the long bones of the extremities, while the vertebral column and the axial skeleton show fairly normal growth and development. Thus, the trunk is long; and except for exaggerated sacrolumbar lordosis, the vertebral column is abnormally erect. The back of the patient is usually flat. In achondroplasia the dwarfism is chiefly appendicular. The long bones of the proximal segments of the extremities —humerus and femur—are conspicuously shortened. The condition is evident at birth and is even recognizable in the fetus. It was known to obstetricians long before it was differentiated as a clinical entity in the adult.

Familial osteochondrodystrophy is not evident at birth. The condition apparently reveals itself at the end of the first year of life, progressing during early childhood and then becoming fixed. The axial skeleton is predominantly affected. The dwarfism is due chiefly to the stunting of growth and the deformation of the vertebral column, thorax and pelvis. The large proximal joints—iliofemoral and scapulohumeral—show a want of osteogenesis associated with an actual destructive process in the cartilage and bone. The roentgenograms reveal a characteristic picture, especially in the pelvis, which is usually narrow; the acetabulum is small and shallow, and the head of the femur is small and often eroded. Usually a subluxation of the joint is present bilaterally. The gait of the patients is greatly impeded thereby and is highly characteristic. The outstanding features are the shortness of the trunk and, especially, of the neck; thus, the head appears sunken between the shoulders, the chin resting on the sternum. The dorsal kyphoscoliosis, the forward protrusion of the sternum and the collapse of the thoracic cage are characteristic.

Mental deficiency is frequent in cases of achondroplasia. In fact, it appears that most persons affected are below par mentally. In cases of Morquio's disease thus far reported the mental deficiency does not figure prominently in the clinical picture. It is likely, however, that as physicians become more familiar with this form of familial dystrophy, the mental defect will be more frequently recognized in these patients.

DISCUSSION

DR. RUDOLPH NEUSTADT: Three and one-half years ago I examined the urine of these 2 patients with Morquio's disease. Edward's showed complete lack of androgens, while Josephine, at that time 18, had an insufficient amount of androgens but a normal amount of estrogens. I am curious to know whether she menstruates.

DR. PAUL I. YAKOVLEV, Waltham, Mass.: Yes, she does. Apparently, neither she nor her brother show any gross hormonal disturbances except that both are retarded in sexual maturation. Both, however, have a low calcium content of the blood. In this, again, they differ from achondroplastic dwarfs.

DR. CLEMENS E. BENDA, Wrentham, Mass: Is Morquio's disease a true malformation?

DR. PAUL I. YAKOVLEV, Waltham, Mass.: Nothing is known of the pathogenesis of this condition, and so the question remains open. There is obviously a familial metabolic disorder, with gross skeletal malformation. Morquio suspected that a neuroregulatory mechanism was involved.

Book Reviews

The Doctor's Job. By Carl Binger, M.D. Price $3. Pp. 423. New York: W. W. Norton & Company, Inc., 1945.

"The Doctor's Job" was written primarily for the laity. It represents an attempt to familiarize them with some of the philosophy of the practice of medicine in the past and at present. As such, it lets some skeletons out of the closet for ventilation. Physicians no longer are represented as God-like, magical creatures with encyclopedic knowledge of all things. Medical ethics, the matter of fees, the problem of the choice of a physician, the advantages and limitations of the family doctor and the role of the specialist are discussed.

Dr. Binger does not believe that magic need be invoked in an intelligent physician-patient relationship. The importance of the transference situation is touched on, and the appeal is for more awareness along these lines and less hocus-pocus.

A review which appeared in the *New York Times* a short while ago stated that the book should have been called "The Psychiatrist's Job." It is true that the book emphasizes the psychiatric implications of all illness. It also presents in some detail the psychosomatic viewpoint, particularly in discussion of peptic ulcer, asthma, hypertension, tuberculosis, etc. The relationship of personality constellation to disease is made relatively simple while remaining good psychiatry.

Dr. Binger is interested, too, in the economic aspects of medical care. Office, hospital and clinic practice are discussed in this frame of reference, and a chapter is devoted to socialized medicine. In general, the views expressed are liberal, yet cautious.

The book has an honest, down-to-earth quality and a fine touch of humor. The psychiatrically trained person will probably learn little from it; the student and general practitioner may learn a great deal, but the book's big contribution is that it should make for a better informed laity, with a healthier conception of the role of their physicians and with some insight into the emotional component of disease.

Peripheral Nerve Injuries; Principles of Diagnosis. By Webb Haymaker, Major, Medical Corps, Army of the United States, and Barnes Woodhall, Lieutenant Colonel, Medical Corps, Army of the United States. Pp. 227, with 225 illustrations. Philadelphia: W. B. Saunders Company, 1945.

War is the time for all good surgeons to come to the aid of the peripheral nerves. Haymaker and Woodhall, in this superbly illustrated small volume, have done a notable service to the surgeon, revising the concepts laid down in the older textbooks of anatomy and surgery and getting away from the static concept that has long been attached to the nervous system. The great collections of cases, clinical records, pathologic tissues and photographs that have been accumulated at the Army Institute of Pathology serve as the basis for the book. Some of the best medical artists in the country have illustrated the text with really lifelike pen and ink drawings. Photographs are abundant.

Section I is devoted to analysis of the segmental and peripheral nerve supply of skin, muscles and skeleton; section II deals with the examination of the peripheral nervous system, and section III discusses injuries of plexuses and peripheral nerves. A fourth section would be desirable but probably cannot be written for years to come. Such a section would deal with restitution and end results of treatment, with serial photographs illustrating the steps of recovery.

The authors have kept their book small in size but large in compass. There are no "case reports," with their irrelevancies and the usual padding. The style is terse, and the illustrations really illustrate.

The Shaping of Psychiatry by War. By John Rawlings Rees, M.D. Price, $2.75. Pp. 158. New York: W. W. Norton & Company, Inc., 1945.

Brigadier John Rawlings Rees, consulting psychiatrist to the British army and medical director of the Tavistock Clinic, London, delivered this material as the Thomas W. Salmon Lectures. He divides his material under four chapter headings, entitled "The Frontiers Extend," "Opportunities Emerge," "The Way Ahead" and "The Tasks of Psychiatry."

Interest in psychiatry was stimulated as a result of World War I, but certainly it has matured more as a result of present war experience than it could have done in years of peace. The author considers the problems of aptitude tests, selection of officer candidates and the study of character stability, personality and leadership. The importance of problems of morale is stressed.

Brigadier Rees emphasizes that psychiatrists, as a result of their war and civilian experience, "have something of value to say in almost every major problem of society—in the planning and maintenance of peace, in the management of nations and in other questions of this magnitude and importance."

In a short appendix, the author outlines the tasks of both military and civilian psychiatry as he envisages the opportunities and responsibilities that lie ahead.

The volume is an illuminating document, full of important data concerning military psychiatric problems. It is highly recommended.

News and Comment

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

At the meeting of the society on May 25, 1944, Paul I. Yakovlev, M.D., president, a symposium was held on the humoral conduction of nerve impulses, and the following papers were read: "Clinical Aspects of Myasthenia Gravis," Henry R. Viets, M.D.; "Electromyographic and Ergographic Studies in Myasthenia Gravis," Mary A. B. Brazier, Ph.D., and "Physiological and Pharmacological Aspects of Neuromuscular Diseases," George H. Acheson, M.D.

Abstracts of the papers with discussions were published in the December 1944 issue of the *Journal of Nervous and Mental Diseases,* pages 613 to 621.

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